F.4

LEAD

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

ATSDR/TP-88/17

TOXICOLOGICAL PROFILE FOR LEAD

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FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 100 most significant hazardous substances was published in the *Federal Register* on April 17, 1987.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

> "(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,
>
> (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and
>
> (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

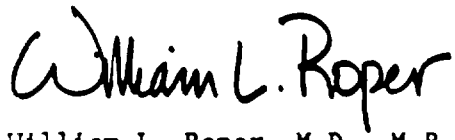
The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Research gaps in toxicologic and health effects information are described in the profile. Research gaps that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



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Disease Registry

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1. PUBLIC HEALTH STATEMENT

1.1 WHAT IS LEAD?

Lead is a naturally occurring bluish-gray metal found in small amounts in the earth's crust. Lead and its compounds can be found in all parts of the environment, for example, in plants and animals used for food, air, drinking water, rivers, lakes, oceans, dust, and soil. Lead in air can be carried long distances from where it is released. Lead in the air attaches to dust. The lead-containing dust is removed from the air by rain. Lead stays in soil for many years. However, heavy rain can cause lead-containing soil to move into water. At this time, lead and lead compounds have been found at 635 out of 1,177 sites on the National Priorities List of hazardous waste sites in the United States. As more sites are evaluated by the Environmental Protection Agency (EPA), this number may change.

Lead used by industry comes from mined ores or from recycled scrap metal. In 1985, 20% of the world's total production of lead was produced by the United States. Lead has a wide range of uses. Its main use is in the manufacture of storage batteries. Other uses include the production of chemicals, including paint, gasoline additives, various metal products (for example, sheet lead, solder, and pipes), and ammunition.

1.2 HOW MIGHT I BE EXPOSED TO LEAD?

You can be exposed to lead and lead compounds from breathing air, drinking water, and eating soil or foods that contain lead. Breathing in air with dust that contains lead or swallowing lead-containing soil such as might be found at a hazardous waste site or near areas with heavy automobile traffic are also sources of exposure. Another source of lead exposure for children is from swallowing nonfood items such as chips of lead-containing paint. This activity is known as pica (an abnormal eating habit). Children who put toys or other items in their mouths may also swallow lead if lead-containing dust and dirt are on these items. Touching dust and dirt containing lead can happen every day, but not much lead passes through the skin. During normal use of lead-containing products, very little skin contact takes place.

The single biggest source of lead in air is from vehicle exhaust. Exposure to lead can also happen while pumping gasoline containing lead additives or from breathing in leaded gasoline fumes. Other sources of release to the air may include emissions from iron and steel production, smelting operations, municipal waste incinerators, and lead-acid-battery manufacturers. Lead is released to the air from active volcanoes, windblown dust, and the burning of lead-painted surfaces. Cigarette smoke is a source of lead, so people who smoke tobacco or who breathe in

tobacco smoke may be exposed to more lead than people who are not exposed to cigarette smoke.

The major sources of lead released to water are lead plumbing and solder in houses, schools, and public buildings; lead-containing dust and soil carried onto water by rain and wind; and wastewater from industries that use lead. Lead is released to dust and soil from such sources as lead-containing waste in municipal and hazardous waste dumps, when fertilizers that contain sewage sludge are used, and from automobile exhaust.

Food and beverages can contain lead if lead-containing dust gets onto crops while they are growing and during food processing. Plants can take up lead from soil such as might be found at a hazardous waste site or near areas with heavy automobile traffic.

Workers may be exposed to lead in a wide variety of occupations including smelting and refining industries, steel welding and cutting operations, battery manufacturing plants, gasoline stations, and radiator repair shops.

1.3 HOW DOES LEAD GET INTO MY BODY?

Lead can enter your body when you breathe in air with lead-containing dust or particles of lead. Almost all of the lead in the lungs enters the blood and moves to other parts of the body. In adults, very little of the amount of lead swallowed in food, beverages, water, and dust or soil enters the blood from the gastrointestinal tract and moves to other parts of the body. However, when children swallow food or soil containing lead such as might be found at a hazardous waste site or chips of lead-containing paint, much more of the lead enters their blood and moves to other body parts. Much less lead enters the body through the skin than through the lungs or gastrointestinal tract. Regardless of how lead enters your body, most of it is stored in bone. Because some lead is stored in the body each time you are exposed, the levels of lead in bone and teeth get higher as a person gets older. Lead that is not stored in the body is removed in the urine and feces.

1.4 HOW CAN LEAD AND ITS COMPOUNDS AFFECT MY HEALTH?

The effects of lead once it is in the body are the same no matter how it enters the body. However, exposure to lead is especially dangerous for unborn children because their bodies can be harmed while they are being formed. If a pregnant woman is exposed to lead, it can be carried to the unborn child and cause premature birth, low birth weight, or even abortion. Young children are at risk because they swallow lead when they put toys or objects soiled with lead-containing dirt in their mouths. More of the lead swallowed by children enters their bodies, and they are more sensitive to its effects. For infants or young children, lead exposure has been shown to decrease intelligence (IQ) scores, slow their growth, and cause hearing problems. These effects can last as children get older and interfere with successful performance in school. These health effects can happen at exposure levels once thought to be safe.

The ability of lead to cause cancer in humans has not been shown. To date, workplace studies do not provide enough information to determine the risk of cancer for workers exposed to lead. However, because laboratory animals fed lead in their diet throughout their lives have developed tumors, lead should be thought of as a probable cancer-causing substance in humans.

Exposure to high levels of lead can cause the brain and kidneys of adults and children to be badly damaged. Lead exposure may increase blood pressure in middle-aged men. It is not known if lead increases blood pressure in women. Also, a couple may have trouble having children if the man is exposed to lead because high levels of lead may affect his sperm or damage other parts of the male reproductive system.

1.5 IS THERE A MEDICAL TEST TO DETERMINE IF I HAVE BEEN EXPOSED TO LEAD?

The amount of lead in the blood can be measured to find out if you have been exposed to lead. Lead in bone and teeth can be measured using X-ray techniques, but this test is not used very often.

Exposure to lead can also be tested by measuring the amount of a substance in red blood cells called erythrocyte protoporphyrin (EP). This method is commonly used to test children for lead poisoning. The level of EP in red blood cells is high when the amount of lead in the blood is high. However, when blood lead levels are not extremely high, EP test results may be within what are considered normal limits. Also, other diseases, like some types of anemias, that affect red blood cells can cause high EP levels.

1.6 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

The graph (Fig. 1.1) on the following page shows the relationship between the amount of lead in the body and known health effects. The amount of lead in the blood is measured in micrograms per deciliter (μg/dL) and is a common way of showing the amount of lead in the body.

In the figure, the column on the left side contains known health effects in laboratory animals and people for exposures of 14 days or less; the column on the right side is for exposures longer than 14 days. Because the levels of exposure to lead that cause damage to a man's reproductive system and the levels that cause abortion in women are not well known, they are not included in the figure.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The Centers for Disease Control (CDC) recommends that screening (testing) for lead poisoning be included in health care programs for children, especially those between the ages of 6 months and 9 years. If a child is found to have high levels of lead (25 μg/dL or greater) and EP (35 μg/dL or greater), medical treatment should be started without delay and the source of the lead exposure should be identified and removed. However, because there is concern that blood lead levels of 10 to 15 μg/dL might cause harm in children, the CDC is currently reviewing their screening level for blood lead.

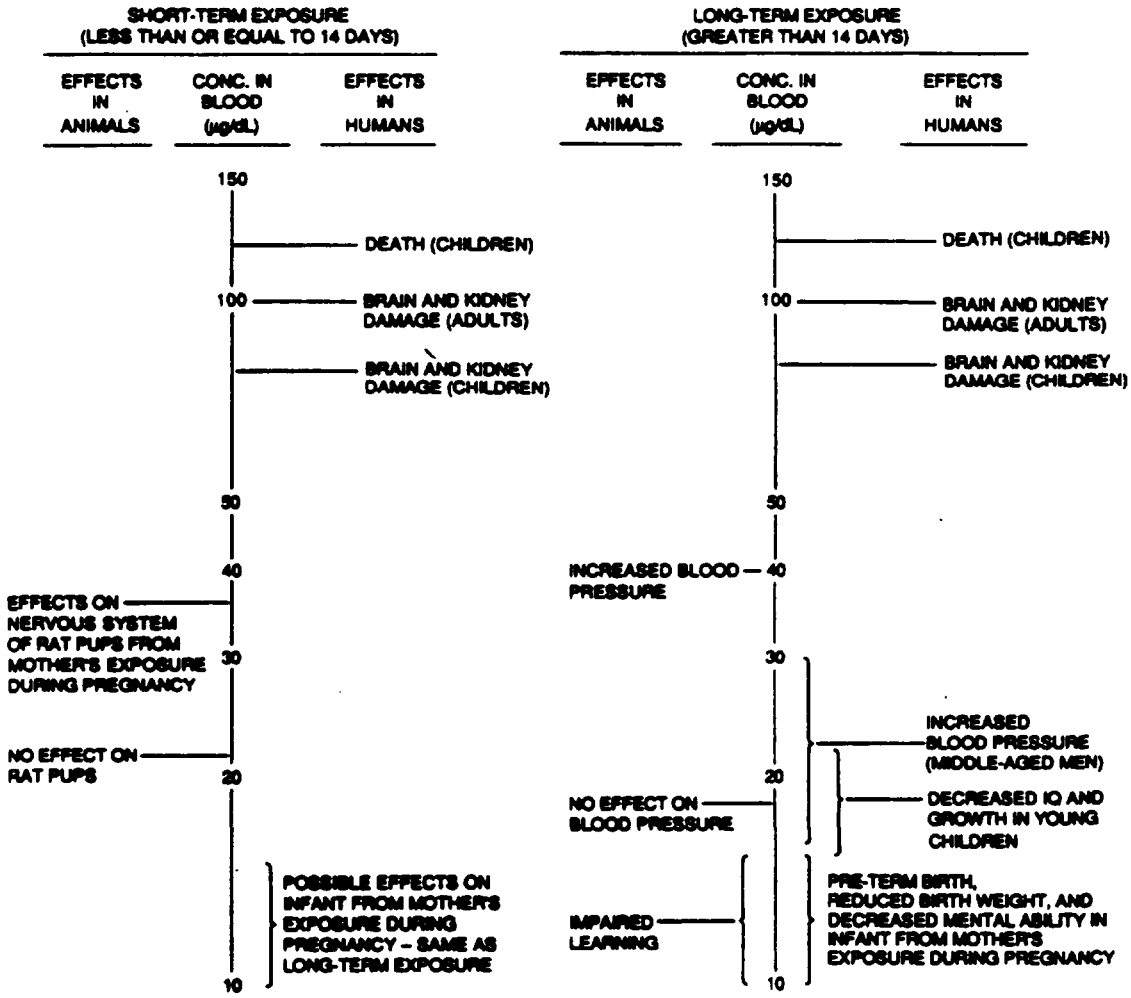


Fig. 1.1. Health effects from ingesting and breathing lead.

To help protect small children who might swallow chips of paint, the Consumer Product Safety Commission (CPSC) does not allow the amount of lead in most paints to be more than 0.06% lead. The CDC suggests that inside and outside paint used in buildings where people live be tested for lead. If the level of lead is high, the paint should be removed and replaced with a paint that contains an allowable level of lead.

The Environmental Protection Agency (EPA) does not allow levels of lead in drinking water to be more than 50 micrograms of lead per liter of water (50 $\mu g/L$). It has been suggested that the amount of lead in drinking water when it leaves the water treatment plant should not be more than 5 $\mu g/L$. The EPA also suggests that public water systems treat their water to decrease contamination from plumbing (pipes, solder, etc.) if the level of lead in tap water that has been standing overnight is more than 10 $\mu g/L$.

The CPSC, EPA, and the states are required by the 1988 Lead Contamination Control Act to test drinking water in schools for lead and to remove the lead if levels are too high. Drinking water coolers must also be lead-free and any that contain lead have to be removed.

To limit the amount of lead people are exposed to in the air, the EPA does not allow the amount of lead that the public breathes over 3 months to be more than 1.5 micrograms of lead per cubic meter of air (1.5 $\mu g/m^3$). The National Institute for Occupational Safety and Health (NIOSH) recommends that workers not be exposed to levels of more than 100 $\mu g/m^3$ for up to 10 hours.

Lead is released to the air with automobile exhaust. Because of this, the EPA limits the amount of lead that can be in leaded gasoline to 0.1 gram of lead per gallon of gasoline (0.1 g/gal), and in unleaded gasoline to 0.05 g/gal.

2. HEALTH EFFECTS SUMMARY

This section will focus on lead in its inorganic form, which is the predominant form of the element in the environment. Data and information about the toxicologic and fate/transport properties of organolead compounds, primarily alkyl lead, are presented in other sections of the document. The data presented in those sections indicate that some of the toxicologic effects of alkyl lead appear to be mediated through metabolism to inorganic lead and that, during the combustion of gasolines containing alkyl lead, significant amounts of inorganic lead are released to contaminate the environment. However, alkyl lead compounds per se do not appear to present a significant problem at waste sites because their use is not likely to result in such disposal. The limited data available on alkyl lead compounds indicate that the toxicokinetic profiles and toxicological effects of these compounds are qualitatively and quantitatively different from those of inorganic lead (EPA 1985a).

2.1 INTRODUCTION

This section summarizes and graphs data on the health effects concerning exposure to lead. The purpose of this section is to present levels of significant exposure for lead based on key toxicological studies, epidemiological investigations, and environmental exposure data. The information presented in this section is critically evaluated and discussed in Sect. 4, Toxicological Data, and Sect. 7, Potential for Human Exposure.

This Health Effects Summary section comprises two major parts. Levels of Significant Exposure (Sect. 2.2) presents brief narratives and graphics for key studies in a manner that provides public health officials, physicians, and other interested individuals and groups with (1) an overall perspective of the toxicology of lead and (2) a summarized depiction of significant exposure levels associated with various adverse health effects. This section also includes information on the levels of lead that have been monitored in human fluids and tissues and information about levels of lead found in environmental media and their association with human exposures.

The significance of the exposure levels shown on the graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of overt clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with frank effects (Frank Effect Level, FEL). Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (Lowest-Observed-Adverse-Effect Level,

LOAEL) or exposure levels below which no adverse effects (No-Observed-Adverse-Effect Level, NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels) are of interest to health professionals and citizens alike.

Adequacy of Database (Sect. 2.3) highlights the availability of key studies on exposure to lead in the scientific literature and displays these data in three-dimensional graphs consistent with the format in Sect. 2.2. The purpose of this section is to suggest where there might be insufficient information to establish levels of significant human exposure. These areas will be considered by the Agency for Toxic Substances and Disease Registry (ATSDR), EPA, and the National Toxicology Program (NTP) of the U.S. Public Health Service in order to develop a research agenda for lead.

2.2 LEVELS OF SIGNIFICANT EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the toxicology data summarized in this section are organized first by route of exposure--inhalation, ingestion, and dermal--and then by toxicological end points that are categorized into six general areas--lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, genetic toxicity, and carcinogenicity. The data are discussed in terms of three exposure periods--acute, intermediate, and chronic.

Two kinds of graphs are used to depict the data. The first type is a "thermometer" graph. It provides a graphical summary of the human and animal toxicological end points (and levels of exposure) for each exposure route for which data are available. The ordering of effects does not reflect the exposure duration or species of animal tested. The second kind of graph shows Levels of Significant Exposure (LSE) for each route and exposure duration. The points on the graph showing NOAELs and LOAELs reflect the actual doses (levels of exposure) used in the key studies. No adjustments for exposure duration or intermittent exposure protocol were made.

Adjustments reflecting the uncertainty of extrapolating animal data to man, intraspecies variations, and differences between experimental vs actual human exposure conditions were considered when estimates of levels posing minimal risk to human health were made for noncancer end points. These minimal risk levels were derived for the most sensitive noncancer end point for each exposure duration by applying uncertainty factors. These levels are shown on the graphs as a broken line starting from the actual dose (level of exposure) and ending with a concave-curved line at its terminus. Although methods have been established to derive these minimal risk levels (Barnes et al. 1987), shortcomings exist in the techniques that reduce the confidence in the projected estimates. Also shown on the graphs under the cancer end point are low-level risks (10^{-4} to 10^{-7}) reported by EPA. In addition, the actual dose (level of exposure) associated with the tumor incidence is plotted.

2.2.1 Key Studies

2.2.1.1 Based on external exposure levels

The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. However, the dose data for humans are generally expressed in terms of internal exposure, usually measured as levels of lead in the blood. Human body burdens of lead result from a combination of inhalation and oral exposure (primarily to inorganic lead). Dose-effect data in terms of external exposure levels or milligrams per kilogram per day (mg/kg/day) doses of lead by a single route of exposure are not generally available for humans. Most of the human data, therefore, cannot be displayed graphically by the methods previously described; these data require a different approach, based on blood lead levels, as described in Sect. 2.2.1.2. Nonetheless, human data are the best basis for any assessment of potential health effects from lead exposure to persons living or working near hazardous waste sites. Experimental studies of lead toxicity in animals provide support for observations in human studies, with some consistency in types of effects and blood-lead-effect relationships; however, animal data on lead toxicity are generally considered less suitable as the basis for health effects assessments than are the human data.

Data concerning dose-effect relationships in animals are available, not only in terms of blood lead levels, but also in terms of external exposure levels or mg/kg/day doses. The animal data can, therefore, be displayed graphically by methods previously described. However, the graphical presentation will be done primarily for consistency with other documents in this series and is not recommended for use in assessing possible health hazards to persons living or working near waste sites. Also, three experimental studies of hematological effects in human adults are available in terms of external exposure levels and are presented with the animal data. Minimal risk levels are not displayed because, as described in Sect. 2.2.1.2 on blood lead levels, no thresholds have been demonstrated for the most sensitive effects in humans.

Exposure data in the following animal studies were converted from dietary or drinking water concentrations to mg/kg/day dosages using EPA (1986b) methods.

Inhalation. The only pertinent dose-effect data found in the available literature were from an unpublished study of hematological effects in humans and a study of the developmental toxicity to animals. Griffin et al. (1975) exposed adult male volunteers to particulate lead at 3.2 or 10.9 $\mu g/m^3$ Pb in air virtually continuously (23 h/day) for 3 to 4 months; after 5 weeks of exposure, erythrocyte levels of delta aminolevulinic acid dehydrase (ALA-D) decreased to ~80 or ~53%, respectively, of preexposure values. Mean blood lead levels increased from 20 $\mu g/dL$ (preexposure) to 27 $\mu g/dL$ at the 3.2-$\mu g/m^3$ exposure level and from 20 $\mu g/dL$ (preexposure) to 37 $\mu g/dL$ at the 10.9-$\mu g/m^3$ exposure level. The 3.2-$\mu g/m^3$ (0.0032-mg/m^3) exposure level is plotted as a LOAEL in Figs. 2.1 and 2.2, but little confidence can be placed in this value because both preexposure and exposure blood lead levels were relatively

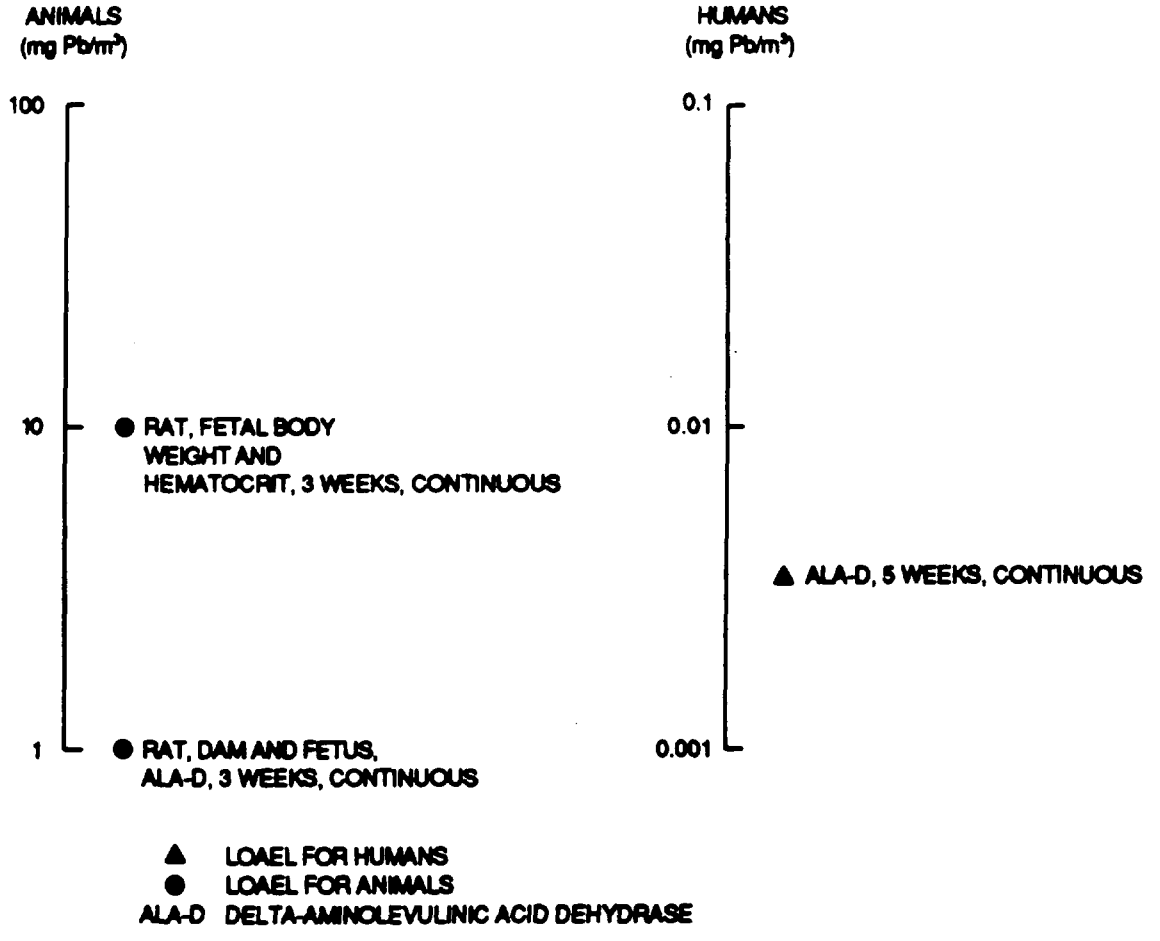


Fig. 2.1. Effects of lead (inorganic)—inhalation exposure.

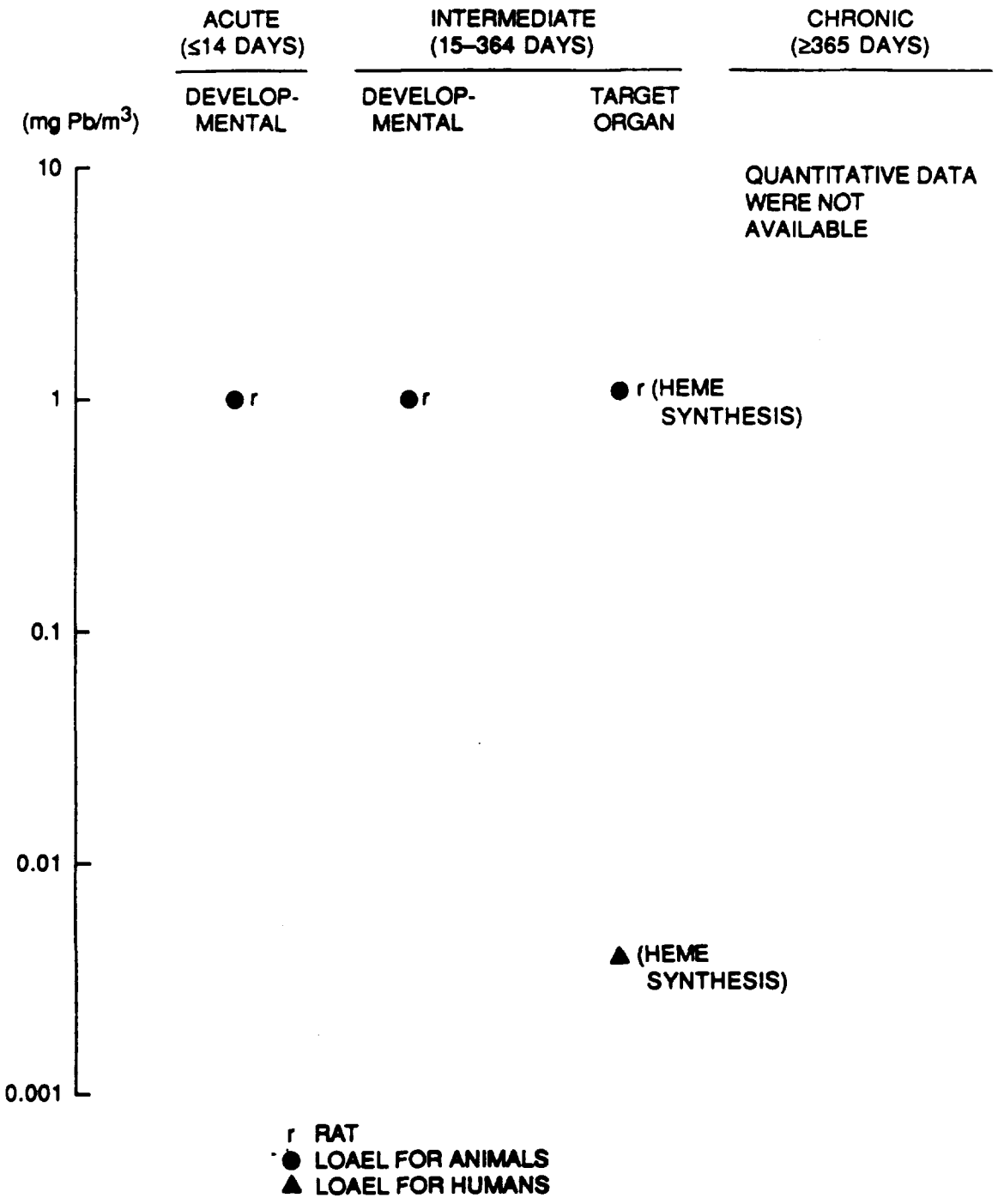


Fig. 2.2. Levels of significant exposure for lead (inorganic)—inhalation.

high; the dose-effect relationship between blood lead and ALA-D has been reported to extend through the lowest blood lead levels detectable, 3 to 5 μg/dL (see Sect. 2.2.1.2 on blood lead levels).

Prigge and Greve (1977) reported that maternal and fetal ALA-D were inhibited in rats exposed to 1, 3, and 10 mg/m^3 Pb throughout gestation (days 1 to 21), and fetal (but not maternal) body weight and hematocrit were decreased at the 10-mg/m^3 Pb level. The inhibition of ALA-D at 1 mg/m^3 is plotted as a LOAEL for target organ effects (heme synthesis) and developmental toxicity in Figs. 2.1 and 2.2. The LOAEL for developmental toxicity is plotted under both acute and intermediate exposure in Fig. 2.2 because it would be of concern for both durations. The effect level for depression of fetal weight and hematocrit, 10 mg/m^3, is also shown in Fig. 2.1.

Oral, lethality. Lethality data for oral exposure, in terms of external dose or exposure level, are limited to LD_{LO} values. The lowest LD_{LO} for the dog is 191 mg/kg Pb; for the guinea pig, it is 313 mg/kg Pb (Sax 1984). These effect levels are displayed in Figs. 2.3 and 2.4.

Oral, systemic/target organ toxicity. The end points of greatest concern for human health, as discussed in Sect. 2.2.1.2, are heme synthesis and erythropoiesis, neurobehavioral toxicity, cardiovascular toxicity, and vitamin D metabolism and growth.

Heme synthesis and erythropoiesis. In humans of both sexes, ingestion of lead acetate at 20 μg/kg/day Pb (0.02 mg/kg/day Pb) every day for 21 days produced a decrease in erythrocyte ALA-D by day 3; the decrease became maximal by day 14 and then remained constant through day 21. An increase in EP (erythrocyte protoporphyrin) occurred in females but not in males 2 weeks after ingestion began. Blood lead levels were ~15 μg/dL before exposure, increasing to ~40 μg/dL after exposure. Increased EP was seen in males at a higher dosage, 30 μg/kg/day Pb (0.03 mg/kg/day Pb), observable after 2 weeks of ingestion (Stuik 1974). Cools et al. (1976) reported similar results in men who ingested lead acetate initially at a dosage of 30 μg/kg/day Pb and then later at 20 μg/kg/day or less as necessary to maintain a blood lead level of 40 μg/dL; the mean preexposure blood lead level was 17.2 μg/dL. The LOAELs from the Stuik (1974) study are shown in Figs. 2.3 and 2.4, but little confidence should be placed in these LOAELs because, as noted in the inhalation study on humans previously discussed, even the preexposure blood lead levels in these studies are relatively high.

In rats fed lead acetate in the diet for 2 years, no effects on heme synthesis parameters were seen at 10 ppm lead (0.5 mg/kg/day Pb) (which did not increase blood lead levels above control values), significant inhibition of ALA-D occurred at ≥50 ppm lead (2.5 mg/kg/day Pb), and significant decreases in hemoglobin level and hematocrit occurred at ≥1,000 ppm lead (50 mg/kg/day Pb) (Azar et al. 1973). In dogs fed lead acetate in the diet, no effects on heme synthesis were seen at ≤50 ppm lead (1.25 mg/kg/day Pb) (Azar et al. 1973). Inhibition of ALA-D occurred at ≥100 ppm lead (2.5 mg/kg/day Pb), and no effect on hemoglobin or hematocrit was seen up through the highest exposure tested--500 ppm lead (12.5 mg/kg/day Pb) (Azar et al. 1973). The NOAELs and LOAELs from this study are shown in Figs. 2.3 and 2.4.

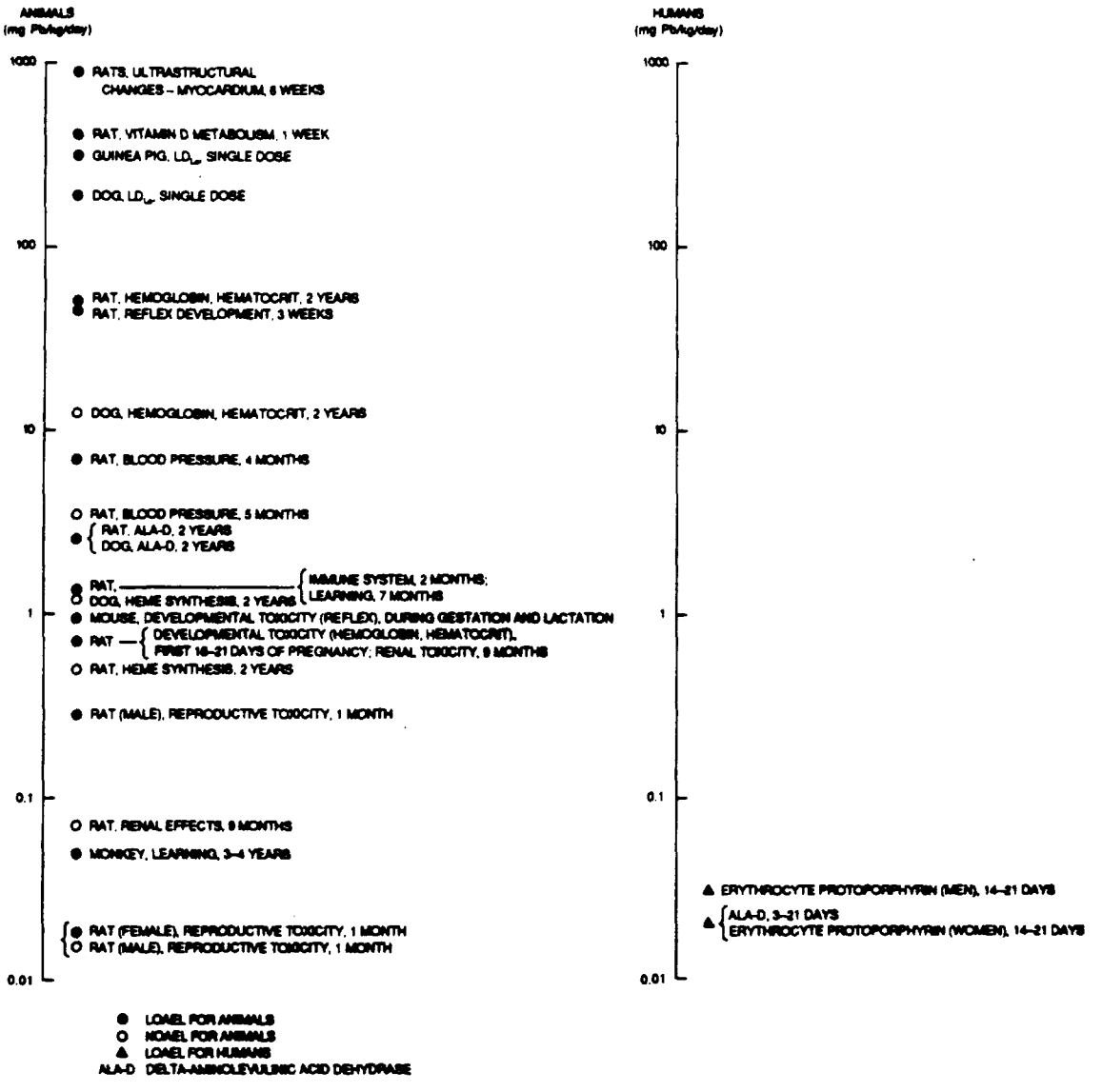


Fig. 2.3. Effects of lead (inorganic)—oral exposure.

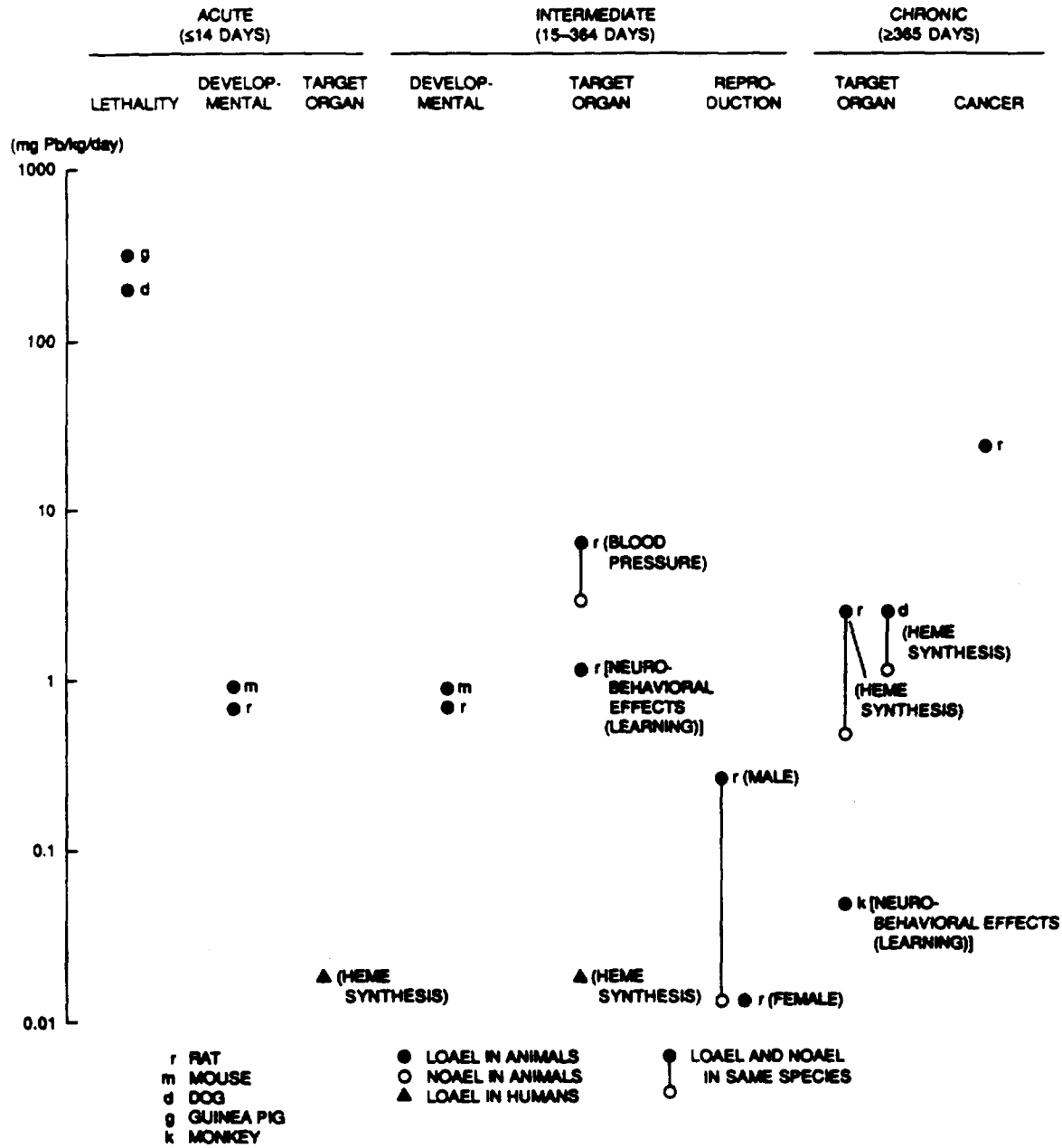


Fig. 2.4. Levels of significant exposure for lead (inorganic)—oral.

Neurobehavioral toxicity. Delays in reflex development were seen in rats treated with 45 mg/kg/day Pb as lead acetate at 3 to 21 days old (~3 weeks) (Kishi et al. 1983). Poorer performance on a spatial discrimination task was reported in rats fed 25 ppm lead (1.25 mg/kg/day) as lead acetate in the diet through 7 months of age (Schlipkoter and Winneke 1980). Monkeys given 0.05 mg/kg/day Pb as a soluble lead compound 5 days/week from birth through testing at 3 to 4, 6 to 7, and 9 to 10 years of age performed significantly less well in learning discrimination-reversal and delayed alternation (Rice 1985a,b; Gilbert and Rice 1987). These values are plotted as LOAELs in Figs. 2.3 and 2.4; NOAELs for these end points were not available.

Cardiovascular effects. In rats administered lead acetate at 25 ppm of lead (3.5 mg/kg/day Pb) in the drinking water for 5 months, there was no effect on blood pressure (Victery et al. 1982). Rats exposed to lead acetate at 50 ppm lead (7 mg/kg/day Pb) in the drinking water for 160 days had markedly increased blood pressures (Iannaccone et al. 1981). The NOAEL and LOAEL are shown in Figs. 2.3 and 2.4. Rats given 1% lead acetate in the drinking water (~6,370 ppm lead, 892 mg/kg/day Pb) for 6 weeks had ultrastructural changes in the myocardium, including myofibrillar fragmentation and mitochondrial swelling (Asokan 1974); this effect level is shown in Fig. 2.3.

Interference with vitamin D metabolism. The only pertinent study reported a depression of plasma levels of 1,25-dihydroxyvitamin D in rats fed lead acetate at 0.82% lead in the diet for 7 days (410 mg/kg/day Pb) (Smith et al. 1981). This effect level is shown in Fig. 2.3.

Effects on growth. A review (EPA 1986a) of 65 pertinent animal studies concluded that low-level exposure to lead during prenatal or early postnatal life results in retarded growth in the absence of overt signs of toxicity; this review did not attempt to establish dose-effect relationships.

Other end points. Other end points in animals for which external dose data are available are renal toxicity, which does not appear to be a sensitive end point for lead toxicity in humans, and immune effects, which have not been observed in immune function studies in humans (adults and children) at blood lead levels higher than those that produced changes in the immune systems of rats. In rats exposed to lead acetate in the drinking water through the dams during gestation and lactation, and then directly until 9 months of age, the NOAEL for renal effects was 0.5 ppm lead (0.07 mg/kg/day Pb), and the LOAEL for renal effects (cytomegaly in the proximal tubule cells) was 5 ppm lead (0.7 mg/kg/day Pb) (Fowler et al. 1980). The NOAEL and LOAEL for renal effects are shown in Fig. 2.3. Rats exposed to lead acetate in the drinking water at 25 ppm lead (1.25 mg/kg/day Pb, LOAEL) (see Fig. 2.3), indirectly through their dams as described above and then directly until testing at 35 to 45 days of age (total ~2 months), had marked depression of antibody responses to sheep red blood cells, decreased serum IgG levels, decreased lymphocyte responsiveness to mitogen stimulation, impaired and delayed hypersensitivity reactions, and decreased thymus weights (Luster et al. 1978, Faith et al. 1979). A NOAEL was not identified.

Oral, developmental toxicity. Twenty-three oral teratogenicity studies in rats and mice have provided no evidence that oral exposure to lead causes malformations.

The offspring of mice treated with lead acetate at 5 ppm lead in their drinking water (0.95 mg/kg/day Pb) during gestation and lactation had delays in the development of the righting reflex (Reiter et al. 1975). Treatment of rats with lead acetate at 5 ppm lead in the drinking water (0.7 mg/kg/day Pb) for the first 18 or 21 days of pregnancy resulted in decreased fetal (but not maternal) hematocrits and hemoglobin levels (Hayashi 1983). These LOAELs are plotted in Figs. 2.3 and 2.4 under both acute and intermediate exposure because they would be of concern for both durations.

Oral, reproductive toxicity. The administration of lead acetate in the drinking water to rats, both indirectly through the dams during gestation and lactation and then directly, produced no effects on females exposed to 5 ppm lead (0.7 mg/kg/day Pb) and delayed vaginal openings in females exposed to 25 ppm lead (3.5 mg/kg/day Pb) (Grant et al. 1980). A lower level of oral dosing with lead acetate, 5 μg lead per day (0.014 mg/kg/day Pb), for 30 days produced higher blood lead levels than in the study by Grant et al. (1980) and caused irregular estrous cycles in female rats and no reproductive effects in male rats (Hilderbrand et al. 1973). Testicular damage was seen in male rats treated orally with lead acetate at 100 μg lead per day (0.29 mg/kg/day Pb) for 30 days (Hilderbrand et al. 1973). The NOAEL and LOAELs from the study of Hilderbrand et al. (1973) are shown in Figs. 2.3 and 2.4.

Oral, genotoxicity. See Sect. 2.2.1.2 for a summary of available data.

Oral, carcinogenicity. In the most adequate study available, rats exposed to lead acetate at 500 ppm lead (25 mg/kg/day Pb) in the diet for 2 years had statistically increased incidences of kidney tumors (Azar et al. 1973). This effect level is shown in Fig. 2.4. The study was not sensitive enough to detect increased incidences of kidney tumors at lower dietary levels.

Dermal. Pertinent dose-effect data were not found in the available literature.

2.2.1.2 Based on blood lead levels

As previously mentioned, the database for lead is unusual in that it contains a great deal of dose-effect data for humans. These data come primarily from studies of occupationally exposed groups and the general population. Most of the exposure or dose data are in terms of internal exposure, usually measured as levels of lead in the blood. Human exposure to lead occurs through a combination of inhalation and oral exposure, with inhalation contributing a greater proportion of the dose for occupationally exposed groups and the oral route contributing a greater proportion of the dose for the general population. As can be seen in Sect. 4.3, the effects of lead are the same regardless of the route of entry into the body, and they are correlated with internal exposure as blood lead level. For these reasons, this section of the profile will not attempt to separate dose data by routes of exposure,

but will present it in terms of blood lead levels. Minimal risk levels are not indicated on figures showing levels of significant exposure, because no thresholds have been demonstrated for the most sensitive effects in humans.

The relationship between environmental lead concentrations and blood lead levels is complex. Slope estimates that predict the increase in blood lead levels that would occur with unit increases in concentrations of lead in air, food, water, and soil are presented in Sect. 2.2.3. In addition, the relative direct (inhaled air) and indirect (ingested dust with lead deposited from air) contributions of air lead to blood lead levels at different air lead levels are tabulated for the calculated typical background levels of lead in food, water, and dust for children in the United States (see Sect. 2.2.3 on Environmental Levels as Indicators for Exposure and Effects). This tabulation is intended to provide an overall perspective on which routes of exposure are most significant in terms of contributions to blood lead levels.

Levels of lead in soil and dust are of particular importance as sources of exposure in children. The CDC (1985) stated that concentrations of lead in soil or dust >500 to 1,000 μg/g result in blood levels in children that exceed background levels.

Lethality. According to the NAS (1972) compilation of data from Chisolm (1962, 1965) and Chisolm and Harrison (1956), death from lead poisoning occurred in children at blood lead levels ≥125 μg/dL. The deaths occurred in children who had severe encephalopathy. The duration of exposure associated with this effect is not clear; however, it seems to have been on the order of a few weeks or more, and, in some cases, it may have been acute. This data point is plotted as a LOAEL for lethality in Figs. 2.5 and 2.6 (acute and intermediate exposure).

Mortality rates (all causes combined) for lead workers exposed occupationally for at least 1 year were slightly but significantly higher than expected (Cooper et al. 1985). Blood lead levels in these workers were 63 μg/dL (battery workers) and 80 μg/dL (production workers). It should be noted that blood lead levels were determined only for some of the men and not for the entire duration of exposure, and control for confounding exposures and smoking was lacking. The lower of the two values is plotted as a LOAEL for decreased longevity--in adults in Figs. 2.5 and under chronic exposure in Fig. 2.6.

Few lethality data are available for animals, and these data either do not include blood lead values (see Sect. 2.2.1.1) or do not clearly indicate a NOAEL or LOAEL (Azar et al. 1973).

Systemic/target organ toxicity. The end points most sensitive to low-level exposure to lead are neurobehavioral deficits and growth retardation in young children and hypertension in middle-aged men. Effects on heme synthesis also occur at very low exposure levels, but there is some controversy as to the toxicological significance of a depression in ALA-D activity in the absence of a detectable effect on hemoglobin levels. The EPA (1986a) and ATSDR (1988) are concerned that the emerging evidence of a constellation of effects, including inhibition of ALA-D activity and pyrimidine-5'-nucleotidase activity and reductions in serum 1,25-dihydroxyvitamin D levels, is indicative that

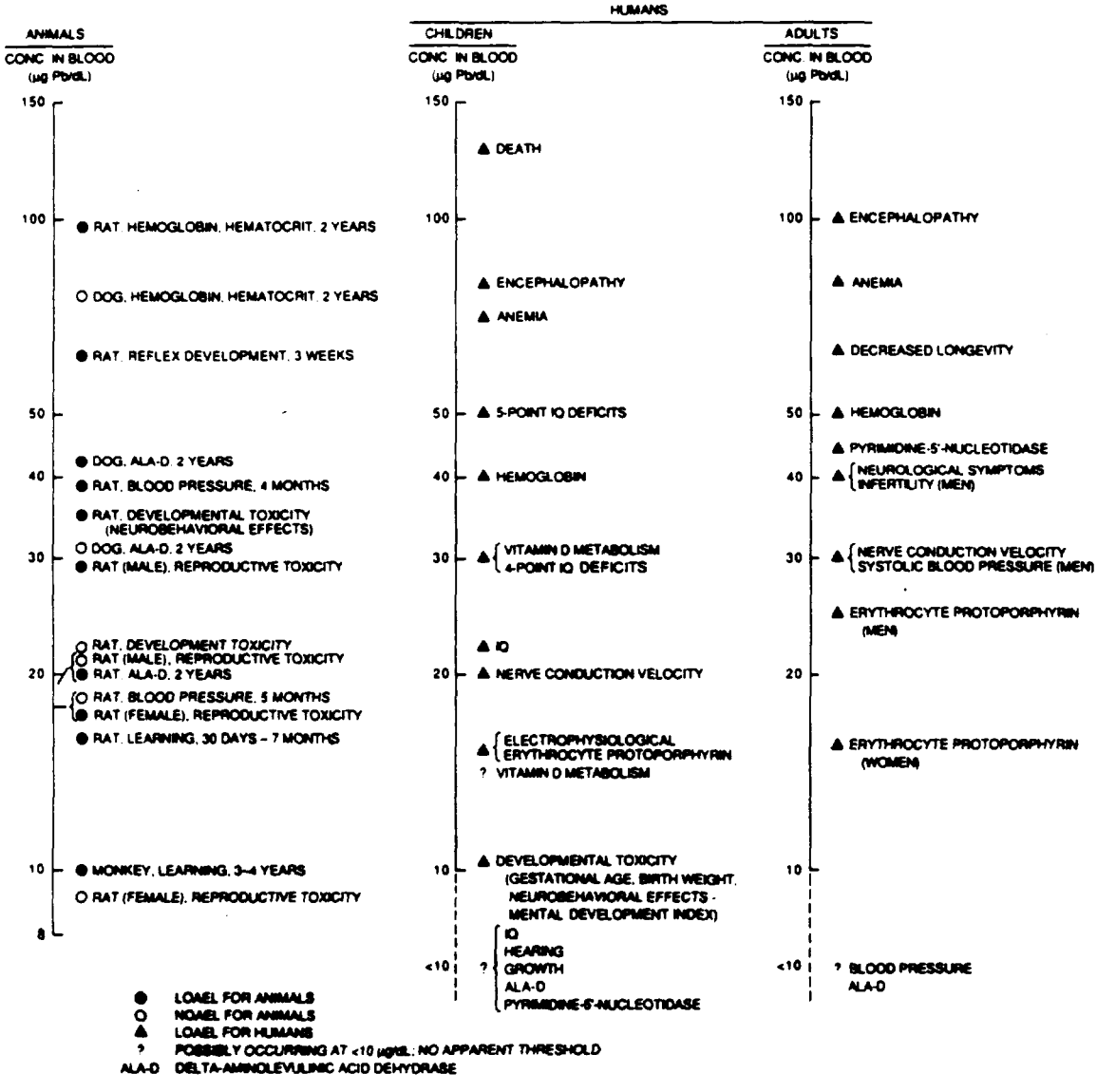


Fig. 2.5. Effects of lead (inorganic)—oral and inhalation exposure.

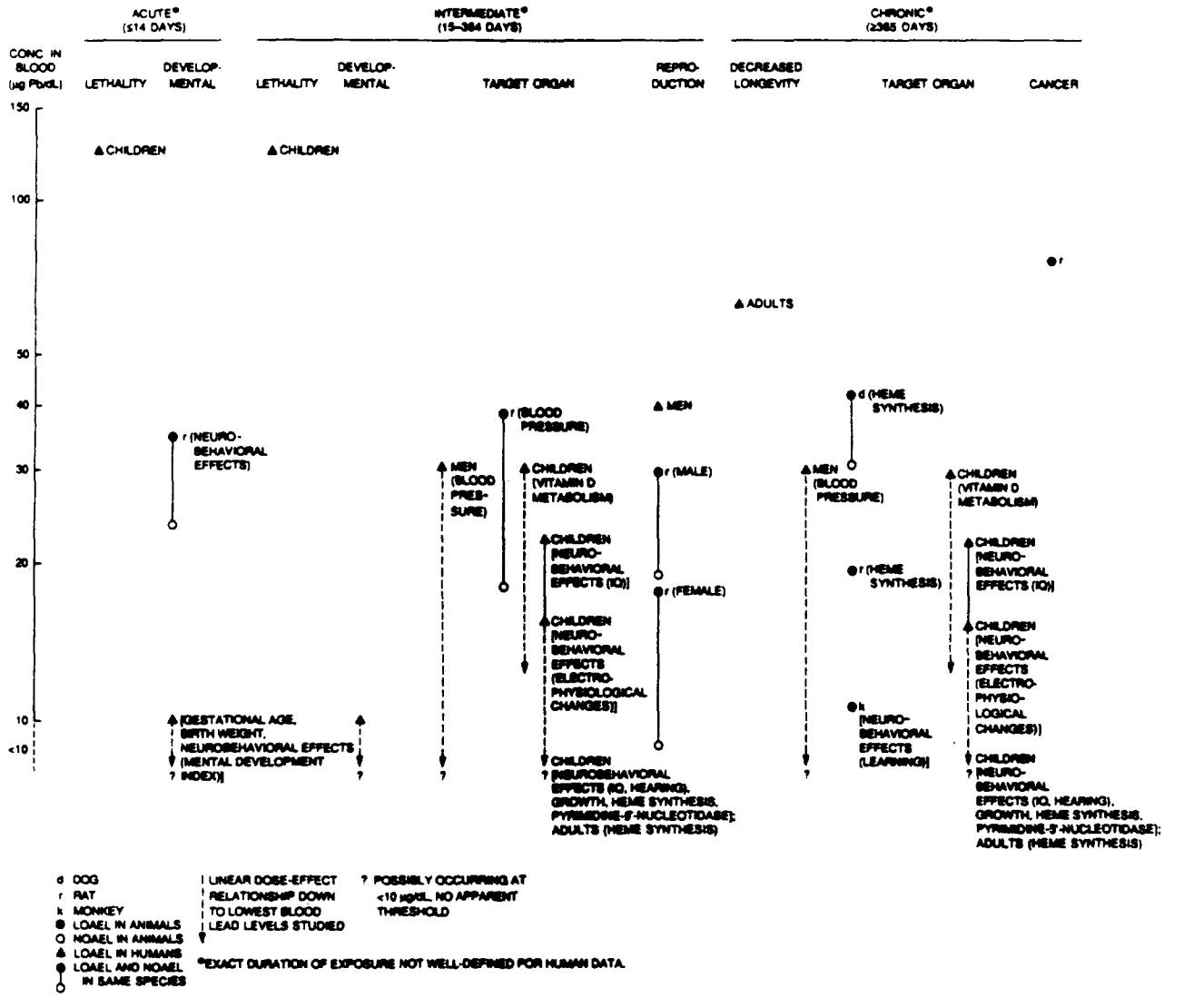


Fig. 2.6. Levels of significant exposure for lead (inorganic)—oral and inhalation.

low-level lead exposure has a far-reaching impact on fundamental enzymatic, energy transfer, and calcium homeostatic mechanisms in the body, which are expressed through subtle effects on neurobehavioral indices, growth, and blood pressure.

Accordingly, this section on systemic/target organ toxicity will deal with the dose-effect data for the following end points: heme synthesis and erythropoiesis, neurobehavioral toxicity, cardiovascular toxicity, and effects on vitamin D metabolism and growth. Dose (as blood lead)-effect data are also available for renal and gastrointestinal effects in humans; these less-sensitive end points are reviewed in Sects. 4.3.2.4 and 4.3.2.8. Although immune system effects have been seen in rats at moderately elevated blood lead levels, the available human data indicate that the immune system is not affected at the same or somewhat higher blood lead levels (see Sect. 4.3.2.7).

Heme synthesis and erythropoiesis. Low-level lead exposure is associated with inhibition of erythrocyte ALA-D activity. The inverse correlation of blood lead level with ALA-D is seen at very low blood lead levels (down to the lowest observed blood lead values of ~3 to 5 μg/dL) and occurs in adults (from both occupationally exposed and the general populations) as well as children (Secchi et al. 1974, Wada et al. 1973, Hernberg and Nikkanen 1970, Chisolm et al. 1985, Roels et al. 1976). This finding is indicated as a LOAEL for ALA-D (see Fig. 2.5) and as the LOAEL for interference with heme synthesis (see Fig. 2.6), possibly occurring at <10 μg/dL. Duration of exposure was intermediate to chronic. ALA-D inhibition has also been reported after acute exposure (Stuik 1974, Cools et al. 1976), but blood-lead-effect relationships for acute exposure are not well established.

Accumulation of EP or ZPP (zinc protoporphyrin) occurs at thresholds of ~25 to 30 μg/dL Pb in men and ~15 to 20 μg/dL Pb in women, based on the evaluation by the EPA (1986a) of a large number of studies of occupationally exposed persons and the general population. The threshold for this effect in children (EPA 1986a, ATSDR 1988, Grant and Davis 1987) is ~15 μg/dL (Roels et al. 1976; Piomelli et al. 1977, 1982; Rabinowitz et al. 1986; Hammond et al. 1985) (and may be lower in the presence of iron deficiency). These values are shown as LOAELs for EP in Fig. 2.5.

The EPA (1986a) concluded that inhibition of erythrocyte pyrimidine-5'-nucleotidase activity may occur in workers at blood lead levels of ≥44 μg/dL, based on the data of Paglia et al. (1975) and Buc and Kaplan (1978). In children, the inverse correlation of blood lead level with the activity of this enzyme continued (without indication of a threshold) down through the lowest blood levels of ~7 μg/dL, based on the data of Angle and McIntire (1978) and Angle et al. (1982). Both values are shown as LOAELs in Fig. 2.5. In Fig. 2.6, the LOAEL for children is shown as the more sensitive effect, possibly occurring at <10 μg/dL, under intermediate and chronic exposure.

High-level exposure to lead results in reduced hemoglobin levels and frank anemia in adults at blood lead levels as low as 50 and 80 μg/dL, respectively (EPA 1986a evaluation of Tola et al. 1973, Grandjean 1979, Lilis et al. 1978, Wada et al. 1973, Baker et al. 1979), and in children at blood lead levels as low as 40 and 70 μg/dL,

respectively (WHO 1977, EPA 1986a evaluation of Adebonojo 1974, Rosen et al. 1974, Betts et al. 1973, Pueschel et al. 1972). These LOAELS for hemoglobin and anemia are depicted in Fig. 2.5.

Dose-effect data for hematological effects in animals are available from the 2-year lead acetate feeding studies of Azar et al. (1973). In the rat, no effects on heme synthesis parameters were seen at the lowest exposure level, 100 ppm lead in the diet, which did not elevate blood lead (11.0 μg/dL) above control levels (12.7 μg/dL). Inhibition of ALA-D occurred at blood lead levels ≥18.5 μg/dL; decreases in hemoglobin level and hematocrit occurred at 98.6 μg/dL. In the dog, no effects were seen on heme synthesis at a blood lead level of 31.5 μg/dL, inhibition of ALA-D occurred at 42.5 μg/dL, and no decrease in hemoglobin or hematocrit was observed even in the highest dosage group, with a mean blood lead level of 75.8 μg/dL. All these values are included in Fig. 2.5, whereas only the NOAEL in dogs and the most sensitive heme effect, ALA-D, are shown in Fig. 2.6 under chronic exposure.

Neurobehavioral toxicity. Based on an evaluation of 28 studies of peripheral nerve function that measured nerve conduction velocity (NCV) in lead workers, the EPA (1986a) concluded that NCV is slowed at blood lead levels <70 μg/dL and possibly as low as 30 μg/dL (Seppalainen et al. 1983). Neurological symptoms occurred in workers with blood lead levels of 40 to 60 μg/dL (Haenninen et al. 1979, Baker et al. 1979, Zimmerman-Tansella et al. 1983). These LOAELs are shown in Fig. 2.5.

In children, neurobehavioral impairment, including IQ deficits of ~5 points, is associated with mean blood lead levels of 50 to 70 μg/dL (de la Burde and Choate 1972, Rummo 1974, Rummo et al. 1979), and IQ deficits of ~4 points are associated with blood lead levels of 30 to 50 μg/dL [estimated from dentine lead values and other data by EPA (1986a)] (Needleman et al. 1979). Significant inverse linear associations between cognitive ability and blood lead, with no evident threshold down to the lowest blood lead levels of ~6 μg/dL, have been reported in two different populations of children (Hawk et al. 1986, Fulton et al. 1987). The mean blood lead level of the highest lead group in the Fulton et al. (1987) study was 22.1 μg/dL, suggesting that IQ deficits are related to lead exposures of <25 μg/dL (ATSDR 1988). Accordingly, 50, 30, 22, and possibly <10 μg/dL are plotted as LOAELs for IQ effects in Fig. 2.5, and the lower two values are shown in Fig. 2.6 for intermediate and chronic exposure. Additional evidence associating neurobehavioral deficits with blood lead values of ~10 to 15 μg/dL (or possibly lower) can be found in the following section on developmental toxicity.

Hearing thresholds in children appear to be adversely affected by lead (Robinson et al. 1985, Schwartz and Otto 1987). Robinson et al. (1985) reported that hearing thresholds increased linearly with maximum historical blood lead levels of 6.2-56.0 μg/dL. In the analysis of NHANES II data by Schwartz and Otto (1987), the probability of elevated hearing thresholds increased with increasing blood lead levels across the entire range of levels studied (<4 to >50 μg/dL). Other electrophysiological changes occur in children at blood lead levels of 15 to 30 μg/dL and possibly lower. These include altered slow-wave voltage during conditioning and altered evoked potentials and NCVs (Otto

et al. 1981, 1982, 1985; Otto 1986; Robinson et al. 1987; Winneke et al. 1984; Landrigan et al. 1976; Schwartz et al. 1988). These values (15 μg/dL for electrophysiological, 20 for NCV, and <10 μg/dL for hearing) are shown in Figs. 2.5 and 2.6 as LOAELs for intermediate and chronic exposure.

High-level exposure to lead produces encephalopathy, a life-threatening condition, in both adults and children. As evaluated by the EPA (1986a), this condition has been noted in some individuals at blood lead levels as low as 100 to 120 μg/dL in adults (Smith et al. 1938; Kehoe 1961a,b,c) and 80 to 100 μg/dL in children (NAS 1972 compilation of data from Chisolm 1962, 1965; Chisolm and Harrison 1956; Smith et al. 1938; Gant 1938; Bradley et al. 1956; Bradley and Baumgartner 1958; Cumings 1959; Rummo et al. 1979). Blood lead values of 100 μg/dL (adults) and 80 μg/dL (children) are shown as effect levels for encephalopathy in Fig. 2.1.

Neurobehavioral effects have been detected in animals at low blood lead levels resulting from the oral administration of lead. Delays in reflex development were seen at blood lead levels of 59 μg/dL in rats treated with lead acetate for ~3 weeks (Kishi et al. 1983). Slower learning and higher rates of inappropriate responses on various reversal and operant learning tasks were observed in rats at blood lead levels as low as 15 to 20 μg/dL (Cory-Slechta et al. 1985, Schlipkoter and Winneke 1980). The treatment duration ranged from 30 days to ~7 months. Impaired learning of discrimination reversal and delayed alternation tasks was observed at 3 to 4, 6 to 7, and 9 to 10 years of age in monkeys at blood lead levels of 10.9 to 15.4 μg/dL (Rice 1985a,b; Gilbert and Rice 1987). The monkeys had received lead acetate from birth through the time of testing. All values (59 μg/dL--rat, reflexes; 15 μg/dL--rat, learning; 10.9 μg/dL--monkey, learning) are plotted as LOAELs in Fig. 2.5. The lowest rat value and monkey value are plotted in Fig. 2.6. Dose-effect data for encephalopathy in animals were not encountered.

Cardiovascular effects. In an evaluation of a number of occupational and general population studies of possible relationships between blood lead levels and hypertension, the EPA (1986a) concluded that levels of ~30 μg/dL were associated with a modest increase in blood pressure, particularly systolic, in men (Weiss et al. 1986, Orssaud et al. 1985, Pocock et al. 1984). Additional evidence, from the NHANES II study (Harlan et al. 1985, Pirkle et al. 1985) and the British Regional Heart Study (Pocock et al. 1984, 1985), indicates small but significant direct associations between blood lead levels and blood pressure in middle-aged men (40 to 59 years old), with no apparent threshold through <10 μg/dL (EPA 1986a). These data are indicated as LOAELs for chronic exposure (see Fig. 2.1 and 2.2).

As presented in the general discussion of cardiovascular toxicity (Sect. 4.3.2.3), there appears to be some consensus that epidemiological studies of the general population indicate that a doubling of blood lead level is associated with an increase of ~1-2 mm Hg in systolic blood pressure, but there is some controversy regarding the inference of a causal relationship between blood lead and blood pressure based on these studies (Victery et al. 1988).

Rats administered lead orally for 4 to 5 months showed no effect on blood pressure at blood lead levels of 18.2 μg/dL (NOAEL) (Victery et al. 1982) and marked increases in both systolic and diastolic pressures at 38.4 μg/dL (LOAEL) (Iannaccone et al. 1981).

Interference with vitamin D metabolism. Rosen et al. (1980) reported that children with blood lead levels >33 μg/dL (LOAEL) have significant depressions in circulating 1,25-dihydroxyvitamin D, the hormonal form of vitamin D. A strong inverse correlation between blood lead levels and serum 1,25-dihydroxyvitamin D was observed over the entire range of blood lead levels measured in the study, 12 to 120 μg/dL. The LOAEL and low end of the correlation range are shown in Figs. 2.5 and 2.6. The evidence indicated that lead interfered with the production of the vitamin D hormone by renal 1-hydroxylase (Rosen et al. 1980, 1981; Mahaffey et al. 1982). Lead's interference with vitamin D metabolism may occur at the level of heme synthesis, since renal 1-hydroxylase is a complex cytochrome P-450 system, of which heme is a constituent (EPA 1986a).

Effects on growth. Analysis of NHANES II data for children ≤7 years old by Schwartz et al. (1986) revealed that blood lead level (range, 4 to 35 μg/dL) was inversely correlated with childrens' height, weight, and chest circumference and was a significant predictor of these growth indices. The strongest association was that of blood lead and height. There was no evidence of threshold through the lowest-observed blood lead concentration. These data are indicated as a LOAEL, possibly occurring at <10 μg/dL.

Additional evidence indicating an inverse relationship between birth weight or postnatal growth and blood lead levels is presented in the following section on developmental toxicity.

Developmental toxicity. The available human data allow no definitive conclusions regarding an association between prenatal lead exposure and congenital anomalies in humans (ATSDR 1988, EPA 1986a, Davis and Svendsgaard 1987). The animal data--one inhalation study and 23 oral studies--indicate that lead compounds are not teratogenic when exposure occurs by natural routes.

Prenatal exposure to lead, however, produces toxic effects on the human fetus, including reductions in gestational age, birth weight, and mental development. These effects occur at relatively low blood lead levels. Moore et al. (1982), McMichael et al. (1986), and Dietrich et al. (1986, 1987b) reported significant inverse correlations between maternal (or cord) blood lead levels and gestational age. Based on risk estimates of McMichael et al. (1986), the risk of preterm delivery increases by approximately fourfold as cord or maternal blood lead level increases from ≤8 to >14 μg/dL. Dietrich et al. (1986, 1987a) and Bornschein et al. (1987) reported a significant inverse association between prenatal maternal blood lead levels and birth weight in the Cincinnati study, with the effect apparent at blood lead levels as low as 12 to 13 μg/dL. Additional follow-up of infants from the Cincinnati study indicated that postnatal growth rates of infants whose mothers had blood lead levels ≥7.7 μg/dL were inversely correlated with postnatal increases in blood lead levels from 3 to 15 months of age (Shukla et al. 1987). The data of Bellinger et al. (1984), while not quite

statistically significant, provide some support for an effect of lead on birth weight, as do the results of Ward et al. (1987), which show statistically significant inverse correlations between placental lead levels and birth weight and head circumference.

Bellinger et al. (1987a) reported significant deficits of 4.8 points on the Bayley Mental Development Index (MDI) at ages 6 to 24 months in children whose blood lead level at birth was 10 to 25 μg/dL, in comparison with children whose blood lead level at birth was <3 μg/dL. These findings are supported by the data of Dietrich et al. (1987a), who reported inverse correlations between prenatal or neonatal blood lead levels (range 1 to ~25 μg/dL) and MDI at 3 or 6 months of age. Additional evidence is provided by the data of Ernhart et al. (1985, 1986) and Wolf et al. (1985), which indicated that neonatal performance on a Neurological Soft Signs scale was related to cord blood lead levels, and that lowered MDI scores at 1 year of age may have been an indirect effect of cord blood lead on Neurological Soft Signs (EPA 1986a, Davis and Svendsgaard 1987). These effects were significantly correlated with cord blood lead levels that averaged 5.8 μg/dL and ranged up to only 14.7 μg/dL. Additional analysis follow-up through 3 years showed an association of maternal (but not cord) blood lead with MDI, PDI, and KID at 6 months (Ernhart et al. 1987). Winneke et al. (1985a,b) found that errors in the Wiener Reaction Performance test were associated with maternal blood lead levels averaging 9.3 μg/dL and cord blood lead levels averaging 8.2 μg/dL; most of the blood lead levels were ≤15 μg/dL. On the basis of this evidence, ATSDR (1988), EPA (1986a), Davis and Svendsgaard (1987), and Grant and Davis (1987) concluded that neurobehavioral deficits and reductions in gestational age and birth weight are associated with prenatal internal exposure levels, indexed by maternal or cord blood lead concentrations of ~10 to 15 μg/dL and possibly lower. The range of 10 to 15 μg/dL (and possibly lower) is shown as a LOAEL for developmental toxicity in Figs. 2.5 and 2.6.

Some of the studies of neurobehavioral and developmental effects discussed in this section on developmental toxicity and in a previous section on neurobehavioral toxicity have been criticized for methodological flaws, including handling of cofactors (EPA 1986a, Ernhart 1988). Additional studies that report no effects at low blood levels have also been criticized for methodological flaws (Needleman 1987, Needleman and Bellinger 1987). ATSDR (1988) and EPA (1986a) have taken criticisms of the positive findings, as well as the existence of negative findings, into account and have concluded that the neurobehavioral and developmental effects seen at low blood lead levels are nonetheless cause for concern.

In rats, significant delays in reflex development occurred in pups whose prenatal and early postnatal exposure level was 35 μg/dL (LOAEL); the NOAEL for this effect was 22 μg/dL (Grant et al. 1980, Kimmel et al. 1980). These points are displayed in Figs. 2.5 and 2.6.

Reproductive toxicity. Lancranjan et al. (1975) and Wildt et al. (1983) studied the fertility of occupationally exposed men. Data from sperm analysis indicated decreased fertility at blood lead levels of 40 to 50 μg/dL (LOAEL), although it was recognized that these studies have

some deficiencies (EPA 1986a). The LOAEL of 40 μg/dL is shown in Figs. 2.5 and 2.6.

Data from older literature indicate that high-level exposure to lead may cause abortion in pregnant women, but the studies were methodologically inadequate and did not provide dose-effect information (EPA 1986a). McMichael et al. (1986) reported a higher incidence of miscarriage and stillbirth among pregnant women living in the lead-smelter town of Port Pirie than in pregnant women living outside the town. Maternal blood lead levels were lower in the cases of stillbirth than in the cases of live birth, but fetal and placental levels in this and another study (Wibberly et al. 1977) were higher than in cases of normal birth.

Data from oral studies in rats indicate the following dose-effect relationships (Figs. 2.5 and 2.6) in terms of blood lead levels: a NOAEL of 9 to 16 μg/dL and a LOAEL of 18 to 29 μg/dL for reproductive effects in females (delayed vaginal opening) (Grant et al. 1980); and a NOAEL of 19 μg/dL and LOAEL of 30 μg/dL for reproductive effects in males (testicular damage) (Hilderbrand et al. 1973).

Genotoxicity. The results for genotoxicity in mammalian systems in vivo and in vitro have conflicted, although the weight of evidence suggests a clastogenic effect of lead (EPA 1986a). Tests for mutagenicity in microbial systems have consistently given negative results, but these systems are not sensitive to other metals that are known carcinogens (EPA 1986a).

Carcinogenicity. Epidemiological studies of lead workers were inadequate to demonstrate or refute the potential carcinogenicity of lead to humans (EPA 1988a).

The EPA (1988a) concluded that lead and inorganic lead compounds are carcinogenic to animals, but that the data are not appropriate for quantitative risk assessment. The most adequate animal study was that of Azar et al. (1973), in which rats exposed to 500 ppm lead in the diet for 2 years had statistically increased incidences of kidney tumors (Azar et al. 1973). The mean blood lead level for this group at 2 years was 77.8 μg/dL (LOAEL; see Fig. 2.4). The study was not sensitive enough to detect increased incidences of kidney tumors at lower dietary levels.

2.2.2 Biological Monitoring as a Measure of Exposure and Effects

As discussed in Sect. 8, lead can be measured in blood, hair, teeth, bones, and urine. The lead level in urine is of questionable value as an indicator of exposure because of the lack of correlation between urinary lead levels and central nervous system (CNS) effects, in addition to the low and variable urinary excretion of lead (Jensen 1984). The Biological Exposure Index (BEI) for lead in urine, which represents a warning level of lead in the urine of exposed workers regardless of whether lead was inhaled, ingested, or absorbed via skin, is 150 μg/g creatine (ACGIH 1987). Hair as an indicator of exposure to lead offers the advantage of being a noninvasive stable medium, but external surface contamination problems are such that it is difficult to differentiate between externally and internally deposited lead (EPA 1986a). The determination of urinary lead following chelation with

calcium disodium EDTA, which mobilizes tissue lead and leads to increased urinary excretion of lead, may be a good indicator of the lead body burden (Janin et al. 1985, Ibels and Pollock 1986), but this test has not been empirically validated. Furthermore, recent work by Cory-Slechta et al. (1987) indicates that diagnostic calcium disodium EDTA chelation may increase the levels of lead in the liver and brain, raising serious concern about continued use of calcium disodium EDTA as a diagnostic tool in children. Since teeth accumulate lead up to the time of shedding or extraction, levels of lead in shed teeth are valuable in assessing exposure at remote time points. The determination of lead in shed teeth, however, is retrospective and of little value in monitoring current exposure. The measurement of lead in teeth in situ may be a more valuable indicator of lead exposure (EPA 1986a). The development of a noninvasive technique using X-ray fluorescence to determine lead in bone (Ahlgren et al. 1976) may prove to be a valuable indicator of the body burden of lead (Jones et al. 1987, Mattson et al. 1987, Rosen et al. 1987, Somervaille et al. 1987). Measurement of lead in blood is the most common method of assessing exposure. The half-life of lead in human blood is 28 to 36 days (Griffin et al. 1975, Rabinowitz et al. 1976); thus, levels of lead in blood reflect relatively recent exposure compared with levels of lead in teeth, which continue to accumulate lead over time. Because lead cycles between the blood and bone, a single blood lead determination cannot distinguish between exposure to a given level for an extended period of time from a previous exposure to a high level that would result in the same blood level due to recycling from bone. As reviewed by EPA (1986a), the relationship of lead levels in air, food, and water to levels in blood is curvilinear, such that the increase in blood concentration is less at high exposure levels than at low exposure levels. This behavior may reflect changes in tissue lead kinetics, reduced lead absorption, or increased excretion, such that blood lead may be an imperfect measure of tissue lead burdens and of changes in tissue levels in relation to changes in external exposure (EPA 1986). Despite the limitations of blood levels in indexing tissue burden and exposure changes, blood lead nevertheless remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to increases in exposure. The BEI for lead in blood of exposed workers is 50 μg/dL (ACGIH 1987). As documented in Sect. 8, the limit for detecting lead in blood in most clinical laboratories is 3 to 5 μg/dL.

Table 2.1, compiled by EPA (1986a), presents the lowest-observed-effect levels in terms of blood lead concentrations associated with particular health effects of concern for human adults. The blood levels represent the threshold for effects seen in at least some adults; therefore, because of individual variations in sensitivity, many individuals may not experience the stated effect until much higher blood levels are reached.

Table 2.2 presents the lowest-observed blood levels associated with a variety of health effects observed in children (EPA 1986a). It is clear from Tables 2.1 and 2.2 that there is a continuum of biological effects associated with lead across a broad range of exposures. Documentation for the dose-effect relationships shown in Tables 2.1 and 2.2 is provided in Sect. 4.3.

Table 2.1. Summary of lowest-observed-effect levels for key lead-induced health effects in adults

Lowest-observed-effect level (PbB)[a] (μg/dL)	Heme synthesis and hematological effects	Neurological effects	Effects on the kidney	Reproductive function effects	Cardiovascular effects
100–120		Encephalopathic signs and symptoms	Chronic nephropathy		
80	Frank anemia				
60				Female reproductive effects	
50	Reduced hemoglobin production	Overt subencephalopathic neurological symptoms		Altered testicular function	
40	Increased urinary ALA and elevated coproporphyrins	Peripheral nerve dysfunction (slowed nerve conduction)			
30					Elevated blood pressure (White males, aged 40-59)
25-30	Erythrocyte protoporphyrin (EP) elevation in males				
15-20	Erythrocyte protoporphyrin (EP) elevation in females				
<10	ALA-D inhibition				?

[a]PbB = Blood lead concentrations.

Source: EPA 1986a.

Table 2.2. Summary of lowest-observed-effect levels for key lead-induced health effects in children

Lowest-observed-effect level (PbB)[a] (μg/dL)	Heme synthesis and hematological effects	Neurological and related effects	Renal system effects	Gastrointestinal effects
80–100		Encephalopathic signs and symptoms	Chronic nephropathy (aminoaciduria, etc.)	Colic and other overt gastrointestinal symptoms
70	Frank anemia			↓
60		Peripheral neuropathies		—
50		↓		
40	Reduced hemoglobin synthesis	? Peripheral nerve dysfunction (slowed NCVs)		
	Elevated coproporphyria	CNS cognitive effects (IQ deficits, etc.)		
	Increased urinary ALA	↓		
30		?	Vitamin D metabolism interference	
15	Erythrocyte protoporphyrin elevation	Altered CNS electrophysiological responses	↓	
10	ALA-D inhibition	↓ MDI deficits, reduced gestational age and birth weight (prenatal exposure)	?	
	↓ Py-5-N[b] activity inhibition	?		
	?			

[a]PbB = Blood lead concentrations.
[b]Py-5-N = Pyrimidine-5'-nucleotidase.

Source: EPA 1986a (with updating).

Several studies have attempted to define the proportion of a population exhibiting effects on heme biosynthesis at a given blood level. Piomelli et al. (1982) analyzed the dose-population response relationship for EP in children, as illustrated in Fig. 2.7. It can be seen that blood lead levels in half of the children showing EP elevations at >1 and 2 SD closely bracket the blood lead level taken at the high end of "normal" (i.e, 30 μg/dL). The dose-response curves for adult men and women, as well as children, prepared by Roels et al. (1976), indicate that the dose response across the blood lead range studied remains greater for children, followed by women, than for men (Fig. 2.8). Elevated EP levels in Fig. 2.8 refer to levels >82 μg/dL erythrocytes. The BEI for EP in blood of workers after 1 month of exposure is 250 μg/dL erythrocytes or 100 μg/dL blood (ACGIH 1987).

Because an elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis, and because contamination problems in measuring blood lead levels exist, the measurement of EP is used for screening asymptomatic children for lead toxicity (CDC 1985, American Academy of Pediatrics 1987). Lead toxicity is generally considered to be present when a blood level of ≥25 μg/dL is associated with an EP level of ≥35 μg/dL. Although the CDC selected 25 μg/dL as a cutoff point for medical referral for screening programs, it did not mean to imply that levels <25 μg/dL are without risk (ATSDR 1988). Proper interpretation of EP data can be made only if iron deficiency is ruled out, because EP can reflect iron deficiency (CDC 1985, Marcus and Schwartz 1987, Mahaffey and Annest 1986). Reliance on EP levels alone for initial screening, therefore, could result in an appreciable number of false negative cases (Mahaffey and Annest 1986).

Calcium disodium EDTA mobilization (provocative test) is also used as a diagnostic tool. The elevated urinary excretion of lead following administration of the chelating agent is presumed to be indicative of an elevated body burden of lead (Cory-Slechta et al. 1987). The CDC (1985) recommended this test to identify children that will respond to chelation therapy, but stated that it should not be used for children with blood lead levels >55 μg/dL; rather, these children should be placed on chelation therapy without the provocative test. Recent results of animal experiments indicate that the use of the chelating agent may increase the levels of lead in the brain, raising serious concern over the continued use of this test (Cory-Slechta et al. 1987). According to ATSDR (1988): "At the same time that progress is being made to reduce some sources of lead toxicity, scientific determinations of what constitute 'safe' levels of lead exposure are concurrently declining even further. Thus, increasing percentages of young children and pregnant women fall into the 'at-risk' category as permissible exposure limits are revised downward. Accompanying these increases is the growing dilemma of how to deal effectively with such a widespread public health problem. Since hospitalization and medical treatment of individuals with Pb-B levels below approximately 25 μg/dL is neither appropriate nor even feasible, the only available option is to eliminate or reduce the lead in the environment."

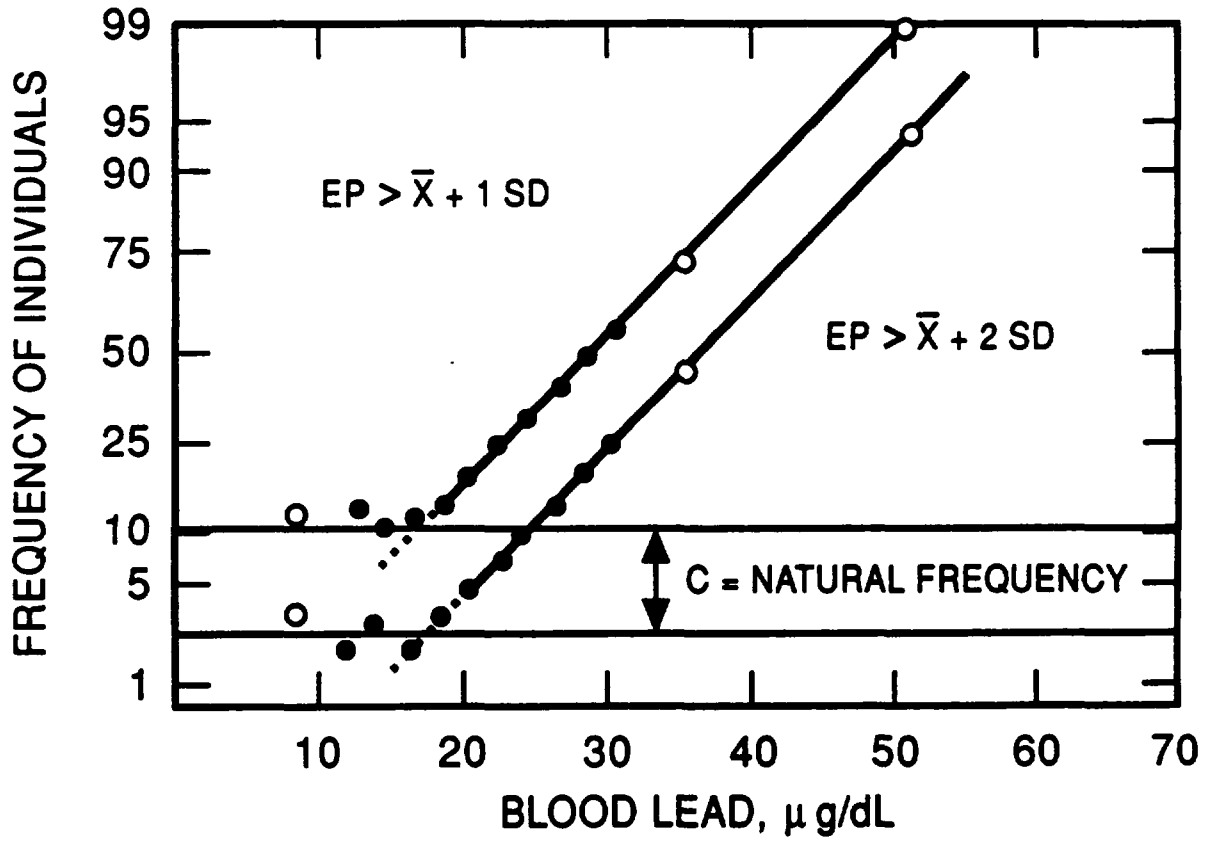


Fig. 2.7. Dose response for elevated erythrocyte protoporphyrin (EP) as a function of blood lead level using probit analysis. Geometric mean plus 1 SD = 33 µg/dL; geometric mean plus 2 SD = 53 µg/dL. *Source:* Piomelli et al. (1982)

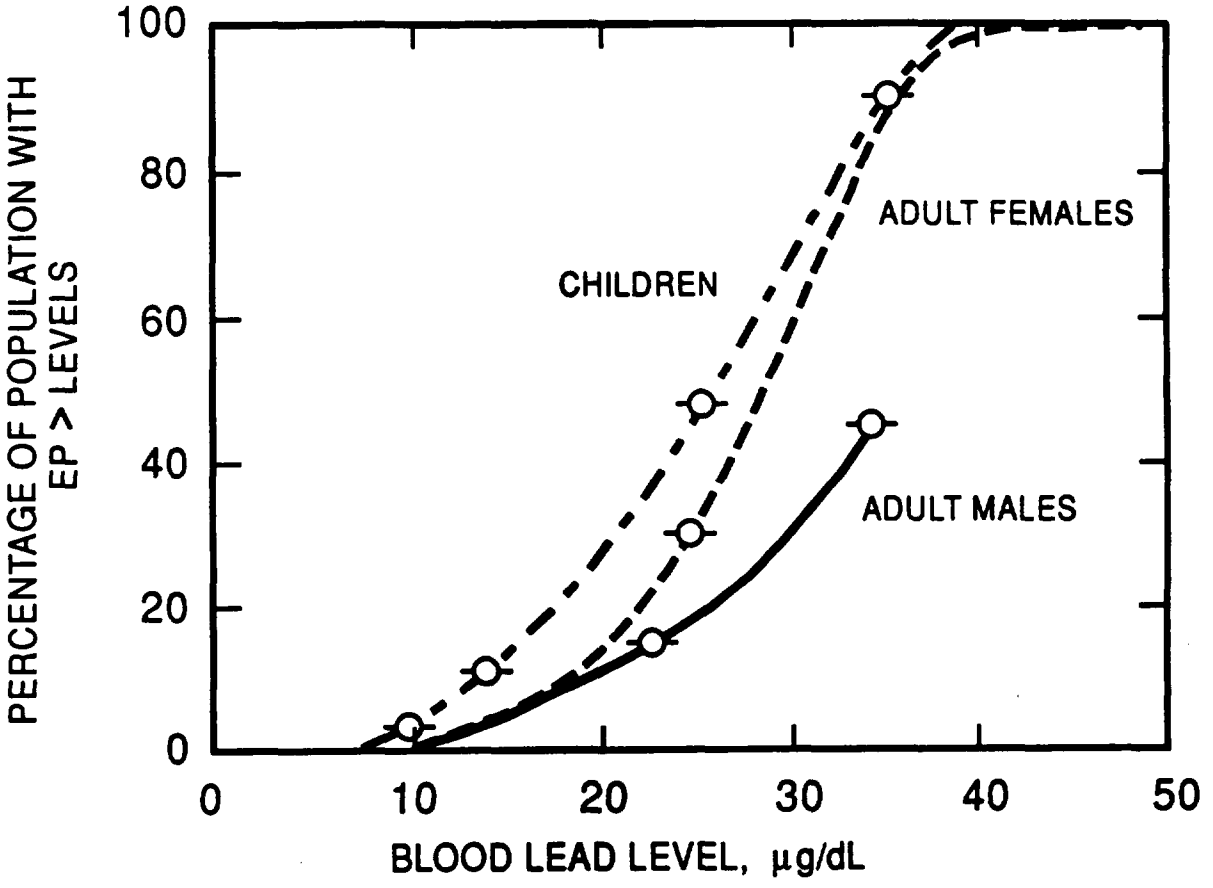


Fig. 2.8. Dose-response curve for erythrocyte protoporphyrin (EP) as a function of blood lead level in subpopulations. *Source:* Roels et al. (1976)

2.2.3 Environmental Levels as Indicators of Exposure and Effects

2.2.3.1 Levels found in the environment

Numerous studies have attempted to correlate ambient air levels of lead with blood levels. A summary of the most appropriate studies is presented in Table 2.3. The slopes calculated from the various studies attempt to predict the increase in blood levels with a unit microgram per cubic meter ($\mu g/m^3$) increase in air concentration (EPA 1986a). At high air concentrations of lead, however, the relationship between the concentration in air and that in blood is nonlinear. At air lead levels of ≤ 3.2 $\mu g/m^3$, there is no statistically significant difference between curvilinear and linear blood lead relationships. Thus, at the range of normal ambient air levels (0.1 to 2.0 $\mu g/m^3$), the relationship appears to be linear. For air lead levels ≥ 10 $\mu g/m^3$, either nonlinear or linear relationships can be fitted. The slope estimates are based on the assumption that an equilibrium level of blood lead is achieved within a few months after exposure begins.

The median blood lead/inhalation slope for children is ~1.92 $\mu g/dL$ blood per $\mu g/m^3$ air, based on three major studies by Yankel et al. (1977), Roels et al. (1980), and Angle and McIntire (1979) (see Table 2.3). The weighted average slope estimate from the data in adult males is 1.64 $\mu g/dL$ blood per $\mu g/m^3$. An "aggregate" slope can also be derived that includes the contribution that air lead makes indirectly to blood lead via dust and soil in addition to inhalation alone. Typical "aggregate" slope values in the range of 3 to 5 $\mu g/dL$ per $\mu g/m^3$ air have been reported (Brunekreff 1984, EPA 1986a). Results of a study by Angle et al. (1984) indicate that the indirect soil/dust contribution to increases in blood lead is 4 to 5 $\mu g/dL$ above the direct inhalation contribution.

Experimental studies relating blood lead levels to dietary lead intake for adults produced slope estimates of an ~0.02 $\mu g/dL$ increase in blood lead per microgram of lead per day total intake (EPA 1986a). When blood lead kinetics were considered, the slope increased to 0.04 $\mu g/dL$ per microgram per day. Estimates from population studies extrapolated to typical dietary intakes yielded a slope of 0.05 $\mu g/dL$ per microgram per day. For infants, the EPA (1986a) calculated a dietary slope of 0.2 $\mu g/dL$ per microgram per day from the study by Ryu et al. (1983).

There is a relatively large degree of variability in the results of several water lead studies (EPA 1986a). Over a wide range of water lead concentrations, the relationship to blood levels is curvilinear; however, at typical ambient water levels in the United States, the relationship appears to be linear. A study by Pocock et al. (1983) determined the relationship at relatively low water lead levels (<100 $\mu g/L$) to be 0.06 $\mu g/dL$ per $\mu g/L$. Lower slope estimates may be more appropriate at higher water lead levels.

Studies relating soil lead to blood lead levels are difficult to compare. The relationship depends on depth of soil lead, sampling method, cleanliness of the home, age of the children, and mouthing activities, among other possible factors. From studies by Yankel et al. (1977) and Angle and McIntire (1979), the EPA (1986a) estimated a concentration increase of 0.6 to 6.8 $\mu g/dL$ in blood lead for each

Table 2.3. Summary of blood inhalation slopes (β)

Population	Study	Study type	N	Slope (β), $\mu g/dL$ per $\mu g/m^3$	Model sensitivity of slope[a]
Children	Angle and McIntire (1979), Omaha, Neb.	Population	1074	1.92	(1.40-4.40)[b,c,d]
	Roels et al. (1980), Belgium	Population	148	2.46	(1.55-2.46)[b,c]
	Yankel et al. (1977); Walter et al. (1980), Idaho	Population	879	1.52	(1.07-1.52)[b,c,d]
Adult males	Azar et al. (1975), five groups	Population	149	1.32	(1.08-2.39)[c,d]
	Griffin et al. (1975), N.Y. prisoners	Experiment	43	1.75	(1.52-3.38)[e]
	Gross (1979)	Experiment	6	1.25	(1.25-1.55)[d]
	Rabinowitz et al. (1973, 1976, 1977)	Experiment	6	2.14	(2.14-3.51)[f]

[a]Selected from among the most plausible statistically equivalent models. For nonlinear models, slope at 1.0 $\mu g/m^3$.
[b]Sensitive to choice of other correlated predictors such as dust and soil lead.
[c]Sensitive to linear vs nonlinear at low air lead.
[d]Sensitive to age as a covariate.
[e]Sensitive to baseline changes in controls.
[f]Sensitive to assumed air lead exposure.

Source: EPA 1986a.

increase of 1,000 μg/g in soil lead. The value from a study by Stark et al. (1982) of 2 μg/dL per 1,000 μg/g may represent a reasonable median estimate. According to CDC (1985), concentrations of lead in soil or dust >500 to 1,000 μg/g result in blood levels in children that exceed background levels.

In order to provide an overall perspective on which routes of exposure are most significant in terms of contributions to blood lead levels seen especially in urban children, the EPA (1986a) has tabulated the relative direct (inhaled air) and indirect (ingested dust with lead deposited from air) contributions of air lead to blood lead at different air lead levels for calculated typical background levels of lead from food, water, and dust for children in the United States (Table 2.4). Calculations and assumptions used in deriving the estimates listed in Table 2.4 are discussed in EPA (1986a). The EPA (1986a) compared the estimated blood lead values, as predicted in Table 2.4 to occur at particular air lead concentrations, with actual blood lead levels observed for children living in the United States in areas having comparable ambient air concentrations and found good agreement, although the actual blood lead levels were slightly higher than predicted.

2.2.3.2 Human exposure potential

Primary and secondary lead smelters and battery plants are the most significant sources of industrial lead emissions into air, ultimately increasing soil and dust lead concentrations in the vicinity. Both adults and, especially, children have been shown to exhibit elevated blood levels when living close to these sources. Likewise, residents of urban areas, particularly children, have been shown to have blood lead levels that are generally higher than levels observed in rural residents. Children ordinarily undergo a stage of development in which they exhibit normal mouthing behavior, as manifested, for example, by thumbsucking, making them at risk of ingesting high levels of lead from dusts and soil that end up on surfaces. An abnormal extension of mouthing behavior known as pica occurs in some children. Pica is the habitual consumption of nonfood items (i.e., paint chips, soil). Much of the lead poisoning attributed to lead-based paints is known to occur because children actively ingest chips of paint (EPA 1986a).

Sources of lead in drinking water are the presence of lead in the raw water supplies and corrosion of plumbing materials in the water distribution system. The major source is corrosion of lead-containing plumbing material. The concentration of lead in the drinking water as a result of corrosion depends on various factors, including the age and the amount of the lead in the plumbing system and the degree of corrosivity of the water. The components of the system that are potential sources of lead include lead goosenecks or pigtails, lead service lines and interior household plumbing, lead solder and fluxes used to connect copper pipes, and alloys containing lead, including some faucets made of brass or bronze. The amount of lead that can enter the water supply from these sources depends on the number and age of lead solder joints and the quality of workmanship of the joints, the contact time between the water and the lead, and the length and diameter of the lead service line. The degree of corrosivity of water depends largely on the pH and the total alkalinity of the water.

Table 2.4. Contributions from various media to blood lead levels (μg/dL) of U.S. children (age = 2 years): background levels and incremental contributions from air

Source	Air lead, $\mu g/m^3$						
	0	0.25	0.50	0.75	1.00	1.25	1.50
Background (non-air)							
Food, water, and beverages	2.37	2.37	2.37	2.37	2.37	2.37	2.37
Dust	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Subtotal	2.67	2.67	2.67	2.67	2.67	2.67	2.67
Background (air)							
Food, water, and beverages	1.65	1.65	1.65	1.65	1.65	1.65	1.65
Ingested dust (with Pb deposited from air)	0.00	1.57	3.09	4.70	6.27	7.84	9.40
Inhaled air	0.00	0.50	1.00	1.50	2.00	2.50	3.00
Total	4.32	6.39	8.41	10.52	12.59	14.66	16.72

Source: EPA 1986a.

2.3 ADEQUACY OF DATABASE

2.3.1 Introduction

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each of the 100 most significant hazardous substances found at facilities on the CERCLA National Priorities List. Each profile must include the following content:

"(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans."

This section identifies gaps in current knowledge relevant to developing levels of significant exposure for lead. Such gaps are identified for certain health effect end points (lethality, systemic/target organ toxicity, developmental toxicity, reproductive toxicity, and carcinogenicity) reviewed in Sect. 2.2 of this profile in developing levels of significant exposure for lead, and for other areas, such as human biological monitoring and mechanisms of toxicity. The present section briefly summarizes the availability of existing human and animal data, identifies data gaps, and summarizes research in progress that may fill such gaps.

Specific research programs for obtaining data needed to develop levels of significant exposure for lead will be developed by ATSDR, NTP, and EPA in the future.

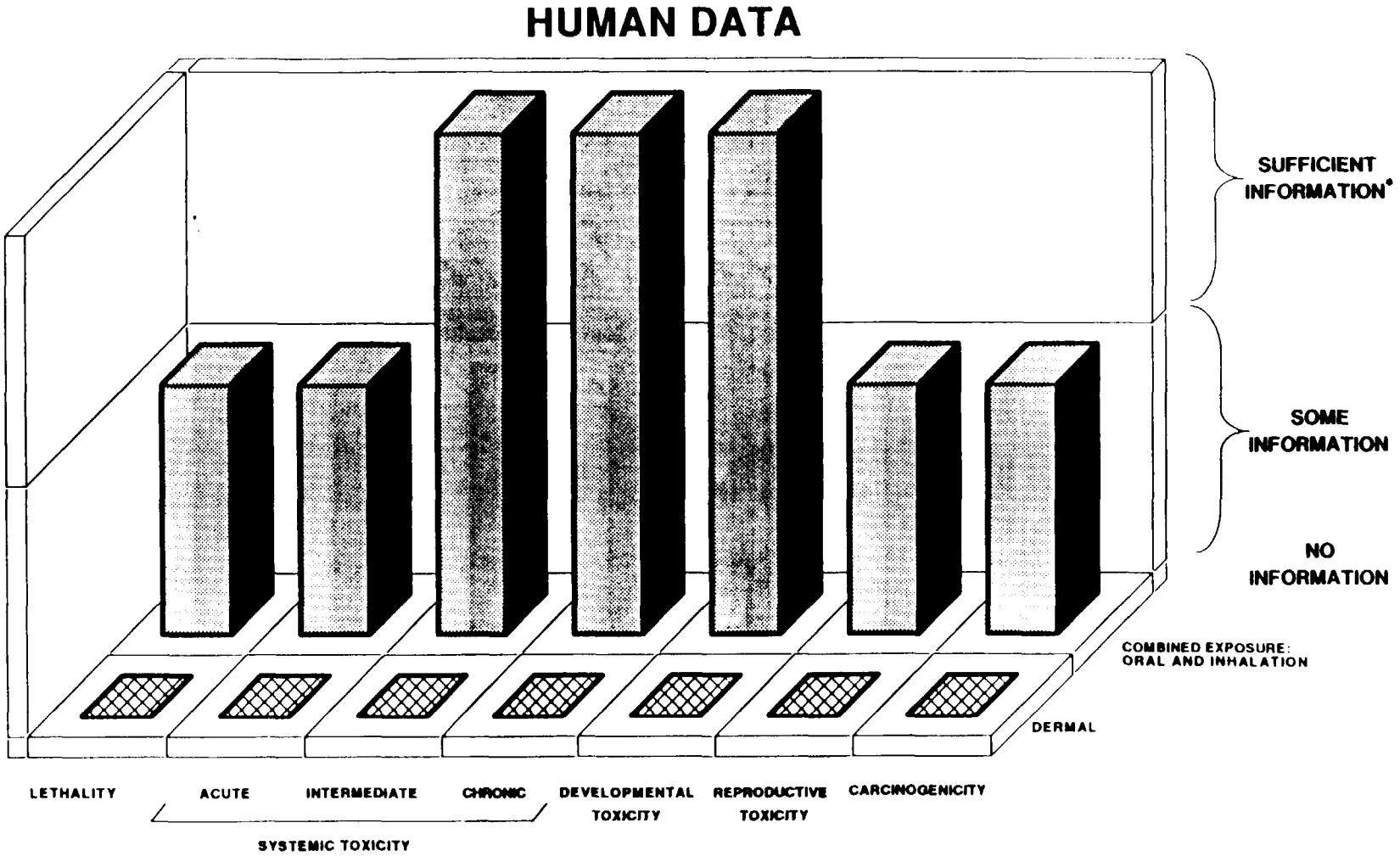
2.3.2 Health Effect End Points

2.3.2.1 Introduction and graphic summary

The availability of data for health effects in humans and animals is depicted on bar graphs in Figs. 2.9 and 2.10, respectively.

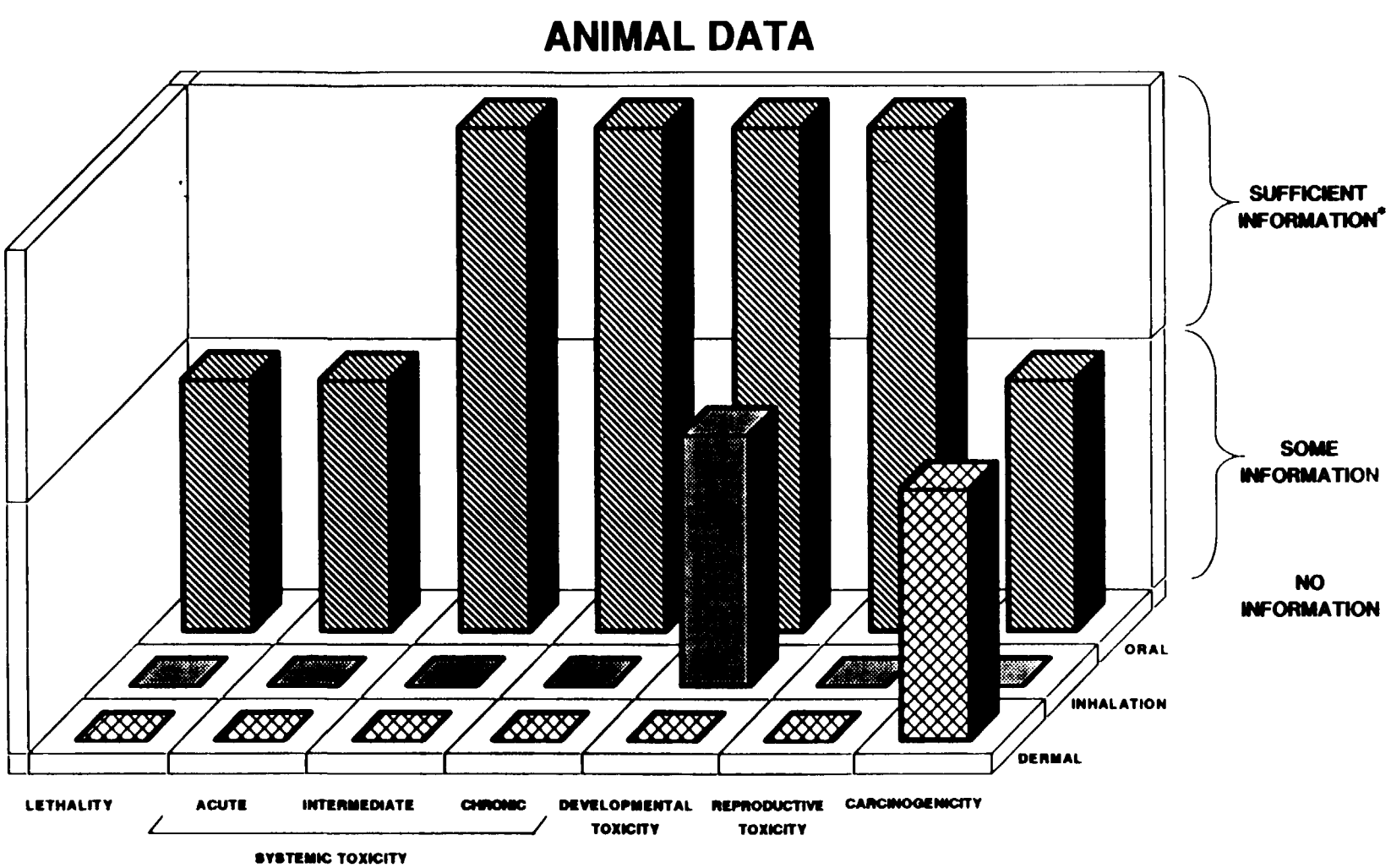
The bars of full height indicate that there are data to meet at least one of the following criteria:

1. For noncancer health end points, one or more studies are available that meet current scientific standards and are sufficient to define a range of toxicity from no-effect levels (NOAELs) to levels that cause effects (LOAELs or FELs).
2. For human carcinogenicity, a substance is classified as either a "known human carcinogen" or "probable human carcinogen" by both EPA and the International Agency for Research on Cancer (IARC)



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.9. Availability of information on health effects of lead (inorganic) (human data).



*Sufficient information exists to meet at least one of the criteria for cancer or noncancer end points.

Fig. 2.10. Availability of information on health effects of lead (inorganic) (animal data).

(qualitative), and the data are sufficient to derive a cancer potency factor (quantitative).

3. For animal carcinogenicity, a substance causes a statistically significant number of tumors in at least one species, and the data are sufficient to derive a cancer potency factor.

4. There are studies which show that the chemical does not cause this health effect via this exposure route.

Bars of half height indicate that "some" information for the end point exists, but does not meet any of these criteria.

The absence of a column indicates that no information exists for that end point and route.

2.3.2.2 Description of highlights of graphs

Because human body burdens of lead are the result of combined oral and inhalation exposure, and dose data are available mainly as blood lead levels rather than as external exposure levels, Fig. 2.9 considers the adequacy of the database for the combined exposure. The potential for dermal exposure/absorption is low, and there are no human data regarding effects from this route of exposure.

Human lethality data are obtained in part from older literature and may suffer from deficiencies in blood lead analyses. The lesser amount of acute exposure data for systemic toxicity in humans is probably a function of the time required for the expression of effects and the usual modes of exposure (occupational and environmental). Intermediate and chronic exposure data for systemic toxicity should be considered together, because length of exposure is frequently not known and distinctions are accordingly somewhat arbitrary. The data for these exposure durations and for developmental toxicity are adequate for defining the most sensitive end points and populations. The data do not clearly indicate NOAELs for humans because associations between blood lead levels and neurobehavioral indices, blood pressure, growth, and basic enzymatic processes, such as heme synthesis, occur over a wide range of blood lead concentrations, with no indication of threshold through the lowest blood lead values encountered.

Data for reproductive toxicity in men indicate that lead may adversely affect testes or sperm at blood lead levels of 40 to 50 μg/dL, but the available studies have deficiencies. Reliable dose-effect data for reproductive effects in women are lacking. Epidemiological studies of lead workers are inadequate for evaluating carcinogenicity to humans (EPA 1988a).

As shown in Fig. 2.10, there are very few animal studies on the effects of inhalation or dermal exposure to lead, and none of these studies provides blood lead data. Adequate animal data, including blood lead levels, are available for oral exposure for systemic toxicity (intermediate and chronic exposure), developmental toxicity, and reproductive toxicity for many of the same end points that are of concern in humans. Data for carcinogenicity indicate that lead compounds are carcinogenic for animals, but the data are not appropriate for quantitative risk assessment (EPA 1988a).

2.3.2.3 Summary of relevant ongoing research

EPA's Office of Health and Environmental Assessment is evaluating the carcinogenicity of lead (EPA 1989b).

More than 100 ongoing federally sponsored projects involving lead toxicity have been identified. Because of the large volume of research under way, only a few representative studies will be selected and discussed.

Several prospective studies of lead exposure and neurobehavioral changes in children are in progress. Alan Leviton of Children's Hospital in Boston is following an initial cohort of children included in the Prenatal Lead Exposure Study to determine the relative prenatal and postnatal contributions of exposures to lead to behavioral, cognitive, and perceptual dysfunctions recognized by teachers when the children are 8 years old, and also to determine the umbilical cord blood and tooth lead levels associated with dysfunctions in school children of that age. Similar work using the same follow-up cohort is being performed by David Bellinger at Children's Hospital in Boston. He is investigating changes in attention, language development, and fine motor function (NTIS 1987). At the University of Cincinnati, Paul Hammond is conducting a large multifaceted study of the health effects of lead on child development, including neurobehavioral, electrophysiological, metabolic, and biochemical components (NTIS 1987). A prospective study in Cleveland by Claire B. Ernhart is sponsored both federally and by the International Lead Zinc Institute (see below).

John Rosen and coworkers at the Albert Einstein College of Medicine (Bronx, New York) are examining neurobehavioral and biochemical effects of lead to discern the efficacy of current treatment guidelines for lead-intoxicated children. This study should provide information on the reversibility of lead effects after chelation therapy and on correlations with X-ray fluorescence measurements of lead in bone, as well as blood lead and chelatable lead levels (Rosen 1987).

I.A. Michaelson of the University of Cincinnati is currently investigating the role of lead on the flow of calcium across the nerve terminal membrane during neonatal CNS development in animals. This work is oriented toward delineating a common mechanism underlying lead-induced CNS neurotransmitter alterations (NTIS 1987).

Donald Fox of the University of Houston has long been involved in investigating lead-induced neurotoxicity of the visual system. His current work deals with delineating, at the cellular level, the alterations in the retinal and cortical receptive field properties that mediate spatial resolution. Similar work is being done at the University of California, Davis, by A.J. Sullivan, who is investigating the effects of lead on the vertebrate photoreceptor (NTIS 1987).

In a National Institute of Environmental Health Sciences-sponsored study, Hemminki of the Institute of Occupational Health in Finland is conducting an epidemiological study to investigate whether exposure to inorganic lead influences pregnancy outcome. In-house studies at NIOSH are under way to assess the association between lead exposure and alterations in semen quality as an indicator of impaired reproductive capacity, to develop new or improved methods of human semen analysis,

and to investigate measures of semen quality that may detect population-based shifts in male reproductive potential. The toxic effects of lead on the hypothalamic-pituitary-testicular axis are being studied by Sokol at the University of California, Los Angeles (UCLA) (NTIS 1987).

In addition to the federally-sponsored research listed above, several ongoing projects are being sponsored by the International Lead Zinc Research Organization, Research Triangle Park, North Carolina (Volpe, 1988). Studies on potential health effects include the following prospective studies on prenatal and postnatal lead exposure: Lead Level and Iron Deficiency in Preschool Years (effect of lead on the development of children) by Claire B. Ernhart, Cleveland Metropolitan Hospital, and Health Effects of Lead in Urban Children by W. G. McBride, Foundation 41, Sydney, Australia (McBride et al. 1987). Additional studies concern serum mineral metabolism and bone mineralization in children by Winston Woo, University of Cincinnati; the relationship between blood lead and blood pressure in industrial workers with fairly stable, low-level lead exposure by Eugene R. Schippen, Exide Corporation, Reading, Pennsylvania; gastric cancer in battery workers by W. Clark Cooper, Lafayette, California; and development of an animal model of lead nephropathy by Harvey Gonick, Cedars-Sinai Hospital, Los Angeles, California.

Additional prospective studies of developmental and neurobehavioral effects of lead in children that are under way in other nations under other sponsorship include those in Port Pirie, Australia (McMichael et al. 1988); Mexico City, New Mexico (Rothenberg et al. 1987); Titova Mitrovica, Yugoslavia (Graziano et al. 1987); Lavrion, Greece (Hatzakis et al. 1987); and Glasgow, Scotland (Moore et al. 1987).

2.3.3 Other Information Needed for Human Health Assessment

2.3.3.1 Pharmacokinetics and mechanism of action

The pharmacokinetic profile of lead in humans is remarkably well understood compared with what is known for other substances, because a number of studies have been conducted using human subjects. Biomonitoring for lead exposure in populations has also provided information that has contributed to the pharmacokinetics of lead in humans. The differences in the distribution of lead between children and adults, however, is not well understood. Further understanding of the distribution of lead and molecular interactions will shed light on the mechanism of lead toxicity.

2.3.3.2 Monitoring of human biological samples

A large database exists regarding blood levels of lead in humans in relationship to effects and levels found in air, diet, drinking water, dust, and soil. Blood levels, however, are an imperfect measure of tissue burden. The monitoring of lead in teeth and bones, in conjunction with blood lead measurements, would provide a better measure of past exposure and body burden; the widespread application of noninvasive X-ray fluorescence has been the subject of recent investigations.

The results of studies comparing blood levels and environmental levels have been used by EPA (1986a) to calculate slopes predicting the increase in blood levels per unit increase in exposure level. These slopes are useful for low exposure levels, but at higher levels the blood-level vs exposure-level curves become nonlinear. Given the uncertainties in quantifying exactly the relationship between lead in a particular environmental medium with blood lead and the number of potential environmental sources, further epidemiological surveys would help to evaluate whether populations have excessive lead burdens. EPA's Office of Air Quality Planning and Standards has developed a multimedia exposure model to evaluate the impacts of alternative lead exposure scenarios in children as part of their review of the National Ambient Air Quality Standard for lead. The EPA has conducted an evaluation and validation of the model to predict daily uptake for young children living near industrial lead sources in terms of ambient air, soil, and dust lead levels that correspond to both historical and current atmospheric lead emission, and also in terms of dietary lead levels from both water and food (EPA 1989b). EPA is continuing to refine the model to provide a flexible tool for a variety of lead-related exposure risk assessments.

2.3.3.3 Environmental considerations

Most of the commonly used analytical methods (e.g., atomic absorption and emission spectrometry, X-ray fluorescence, and electrothermal methods) have the required sensitivity and adequate specificity to measure lead levels in most environmental media. In certain cases, lead concentrations in the blank become the limiting factors in a method's lowest detection limit. With analytical techniques available today, the level of organic lead in air in rural areas can barely be measured (Berg and Jonsson 1984). One of the commonly used methods, inductively coupled plasma/atomic emission spectroscopy, does not provide adequate sensitivity to determine lead levels in foods (EPA 1986a). Most of the analytical methods cannot directly identify the various lead compounds. Both electron microprobe and X-ray diffraction techniques have been used to identify lead compounds in environmental samples (EPA 1986a).

As a result of stepwise reductions in the amount of lead used in gasoline in recent years, air monitoring data from as recent as 1984 may not be adequate in describing current ambient levels, and data for levels of lead currently in the atmosphere were not available. Lack of current data is believed to be due to publishing delays rather than the lack of ongoing research.

Although significant data on the physical processes leading to the transport of lead from one environmental medium to another are available, data on its chemical fate are limited. Even the nature of chemical species present in the various media under given conditions are not known with certainty. Therefore, it is expected that uncertainties exist in the estimated data pertaining to the fate and transport of lead in the environment.

Interactions between lead and other environmental pollutants have been postulated. For example, lead is speculated to form lead sulfate

under certain conditions in both air and water in the presence of the sulfate ion (EPA 1986a).

To improve the understanding of the adsorption of lead to soil, the federal government is currently sponsoring five research projects to study the soil properties that affect sorption of lead to soil (NTIS 1987).

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical identity of lead is given in Table 3.1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical properties of lead and a few of its compounds are listed in Table 3.2. Metallic lead is stable in dry air; however, in moist air, it quickly forms lead monoxide, which in turn produces lead carbonate with carbon dioxide in air. In general, the chemical properties of inorganic lead compounds are similar to those of the alkaline earth metals. The nitrate, chlorate, and acetate salts are water soluble; the chloride is slightly soluble; and the sulfate, carbonate, chromate, phosphate, and sulfide are insoluble. The chromate, carbonate, nitrate, sulfide, and phosphate are soluble in acid, and the chloride is slightly soluble in acid (Weast 1985). Lead forms stable tetraalkyl compounds with organic ligands, for example, tetramethyl, tetraethyl, tetrapropyl, and tetrabutyl compounds. They are soluble in many organic solvents but are insoluble in water. The tetraorganolead compounds decompose to lead metal and free organic radicals at elevated temperatures or in the presence of light. In the presence of oxygen, the thermal decomposition of tetraethyl lead produces lead oxide rather than the free metal. Lead also forms stable metal complexes with polydentate chelating agents, for example, penicillamine or EDTA (Carr 1981; EPA 1985a, 1986a).

Table 3.1. Chemical identity of lead

Synonyms	Lead metal Plumbum Pigment metal
Trade name	C.I. 77575; Lead S2;50
Chemical formula	Pb
Wiswesser line notation	PB
Crystalline structure	Face-centered cubic
Identification numbers	
CAS Registry No.	7439-92-1
NIOSH RTECS No.	OF7525000
EPA Hazardous Waste No.	Not available
OHM-TADS No.	7216776
DOT/UN/NA/IMCO Shipping No.	Not available
STCC No.	Not available
Hazardous Substances Data Bank No.	231
National Cancer Institute No.	Not available

Source: HSDB 1987; IARC 1980.

Table 3.2. Physical properties of lead and a few compounds

	Lead (Pb)	Lead acetate [$Pb(CH_3C00)_2$]	Lead chloride ($PbCl_2$)	Lead chromate ($PbCrO_4$)	Lead nitrate [$Pb(NO_3)_2$]
CAS No.	7439-92-1	301-04-2	7758-95-4	7758-97-6	10099-74-8
Atomic/molecular weight	207.2	325.29	278.11	323.19	331.21
Color	Bluish-gray	White	White	Yellow	Colorless
Physical state	Solid	Solid	Solid	Solid	Solid
Odor	None	NA[a]	NA	NA	NA
Melting point, °C	327.4	280	501	844	Decomposes at 470°C
Boiling point, °C	1770	NA	950	Decomposes	NA
Autoignition temperature	NA	NA	NA	NA	NA
Solubility					
Water	Insoluble	44.3 g/100 mL at 20°C	0.99 g/100 mL at 20°C	58 µg/L at 25°C	37.65-56.5 g/100 mL at 0°C
Organic solvents	Insoluble	Soluble in glycol	Insoluble in ethanol	Insoluble in acetic acid	Slightly soluble in dilute ethanol
Density, g/cm^3	11.35 at 20°C	3.25 at 20°C	5.85	6.12 at 15°C	4.53 at 20°C
Partition coefficient	NA	NA	NA	NA	NA
Vapor pressure, mm of Hg	1.0 at 980°C	NA	1 at 547°C	NA	NA
Henry's law constant	NA	NA	NA	NA	NA
Refractive index	2.01	NA	2.199-2.260	2.31-2.66	1.782
Flashpoint	NA	NA	NA	NA	NA
Flammability limits	NA	NA	NA	NA	NA
Conversion factors					
Air	[b]	[b]	[b]	[b]	[b]
Water	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL
Solid	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g

Table 3.2 (continued)

	Lead oxide (PbO)	Lead sulfate ($PbSO_4$)	Tetraethyl lead [$(C_2H_5)_4Pb$]	Tetramethyl lead [$(CH_3)_4Pb$]	Triethyl lead chloride [$(C_2H_5)_3PbCl$]
CAS No.	1317-36-8	7446-14-2	78-00-2	75-74-1	1067-14-7
Molecular weight	223.20	303.26	323.45	267.35	329.85
Color	Yellow	White	Colorless	NA	NA
Physical state	Solid	Solid	Liquid	Liquid	NA
Odor	NA	NA	NA	NA	NA
Melting point, °C	886 (Litharge)	1170	−136	−27.5	NA
Boiling point, °C	Decomposes at 1472	NA	Decomposes at 198-202	Decomposes at 110	NA
Autoignition temperature	NA	NA	NA	NA	NA, but when heated it emits toxic fumes of Pb and chlorine
Solubility					
Water	17 mg/L at 20°C	42.5 mg/L at 25°C	0.8 mg/L at 20°C	9 mg/L	NA
Organic solvents	NA	NA	Soluble in benzene and petroleum ether	NA	NA
Density, g/cm^3	8.0 (Massicot) 9.53 (Litharge)	6.2	1.6528 at 20°C	1.995 at 20°C	NA
Partition coefficient	NA	NA	NA	NA	NA
Vapor pressure, mm of Hg	NA	NA	0.15-0.30	22.5	NA
Henry's law constant	NA	NA	NA	NA	NA
Refractive index	2.51-2.71	1.822-1.894	1.5195 at 20°C	1.5128 at 20°C	NA
Flashpoint	NA	NA	NA	NA	NA
Flammability limits	NA	NA	NA	NA	NA
Conversion factors					
Air	*b*	*b*	1 ppm = 10.42 mg/m^3 as lead	1 ppm = 8.61 mg/m^3 as lead	1 ppm = 10.62 mg/m^3 as lead
Water	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL	1 ppm (w/v) = 1 mg/L = 1 µg/mL
Solid	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g	1 ppm (w/w) = 1 mg/kg = 1 µg/g

[a]NA = Not applicable.
[b]Since these compounds exist in the atmosphere in the particulate state, their concentrations are expressed as $\mu g/m^3$ only.

Source: Weast 1985; McCormack et al. 1981; Carr 1981; Howe 1981; Windholz 1983; EPA 1985a, 1986a; IARC 1980; Sax 1984.

4. TOXICOLOGICAL DATA

4.1 OVERVIEW

Absorption of airborne lead by inhalation first involves deposition of particulate lead in the respiratory tract. Once lead is deposited in the respiratory tract, its absorption by humans and animals is virtually complete. Humans ingest lead by consuming lead-containing food and beverages and by swallowing lead deposited in the upper respiratory tract. Through normal mouthing activity and pica (abnormal eating), children may ingest lead from such sources as dirt, dust, and paint chips. The primary site of lead absorption in children is the gastrointestinal tract.

Dermal absorption of lead by humans is reported to be much less significant than absorption by inhalation or oral routes of exposure.

Rather than being homogeneously distributed in the body, lead is dispersed among several physiologically distinct compartments. A physiologically based model based on data in humans predicts the distribution of lead into three compartments: blood, soft tissue, and bone. The lead in each of these compartments has a different rate of intercompartmental movement and residence time.

In human adults, ~95% of the total body burden of lead is found in the bones. Two physiologically distinct pools of lead are present in bone: (1) an inert pool with a half-life of decades and (2) a labile component that readily exchanges lead between bone and blood or soft tissue. Bone lead distributes to the teeth as well. Tooth lead levels have been shown to increase with age and also with degree of exposure.

Of the lead distributed in the blood compartment in humans, 99% is associated with the erythrocytes. The remaining 1% is in plasma and is available for transport to soft tissues. Over 50% of the erythrocyte lead pool is bound to hemoglobin. A curvilinear relationship between blood lead levels and plasma lead levels has been observed and shows that the fraction of lead in the plasma increases nonlinearly at blood lead levels above ~40 μg/dL.

In humans, lead accumulation in most soft tissues such as kidney, liver, and brain, with perhaps the exception of the renal cortex and aorta, is of a much smaller proportion than accumulation in bones. Lead is readily distributed to the fetus.

In humans or animals, any dietary lead not absorbed by the gastrointestinal tract is eliminated in the feces. Airborne lead that has been swallowed and not absorbed is eliminated in a similar fashion. The blood lead that is not retained is either excreted by the kidney or excreted through biliary clearance into the gastrointestinal tract.

Humans are usually exposed to lead by the inhalation and oral routes, with occupationally exposed populations receiving a greater proportion of their exposure through inhalation and with the general population receiving a greater proportion through the oral route. The effects of exposure to lead, however, do not appear to depend on the route of entry, but rather are correlated with internal exposure, usually measured as blood lead levels.

At high exposure levels, lead produces encephalopathy, gastrointestinal effects (colic), anemia, nephropathy, and electrocardiographic abnormalities in humans. Untreated encephalopathy is frequently fatal. These effects are generally seen only in occupationally exposed populations and in children, particularly children who ingested chips of lead paint and old plaster or who live in environments contaminated by dust and flecks from deteriorating lead paint. In addition, high exposure to lead may cause spontaneous abortion in women and decreased fertility in men.

Lower-level exposure to lead affects the synthesis of heme, which is a constituent not only of hemoglobin, but also of cytochrome P-450 and electron-transfer cytochromes. Hence, effects on heme synthesis can have pronounced effects on fundamental metabolic and energy-transfer processes.

In addition, lower-level exposure to lead decreases the circulating levels of an active form of vitamin D, 1,25-dihydroxyvitamin D, in children. This form of vitamin D is largely responsible for the maintenance of calcium homeostasis in the body.

Effects of great concern from low-level exposure to lead are neurobehavioral effects (including MDI and IQ deficits and elevated hearing thresholds) and growth retardation in infants exposed prenatally and children exposed postnatally, and the elevation of blood pressure in middle-aged men. Dose-effect relationships for these effects show no indications of a threshold down to the lowest levels of internal exposure (blood lead levels <10 μg/dL).

Because lead accumulates in bone, from which it can be mobilized and redistributed in the body, past cumulative exposure contributes to the risk. The physiological stress of pregnancy can mobilize lead from maternal bone, resulting in greater exposure of the fetus, because there is no barrier to the uptake of lead by the fetus.

Experimental studies of the systemic toxicity of lead to animals provide support for the observations in human studies, both in terms of the types of effects and the dose (as blood lead)-effect relationships.

Data regarding the genotoxicity of lead compounds are ambiguous. Results of mutation tests in microorganisms were negative, but these tests may not be appropriate to demonstrate the mutagenicity of carcinogenic metals. Results in mammalian test systems and in vivo studies in occupationally exposed humans were conflicting, but the data do suggest clastogenic effects.

Occupational studies of lead production and battery workers weakly associate exposure to lead with increased risk of cancer, particularly of the respiratory and digestive tracts. These studies were considered

to provide inadequate evidence of carcinogenicity of lead to humans because of lack of control or adjustment for exposure to other chemicals and for smoking and because of the lack of dose-response relationships. Rats treated orally or parenterally with soluble lead compounds show significantly increased incidences of kidney tumors.

4.2 TOXICOKINETICS

4.2.1 Absorption

The rate and degree of absorption of a compound are largely related to its solubility in body tissues and fluids, among other factors. In addition to exposure to the elemental form of lead, the potential also exists for human exposure to lead compounds, each of which has unique solubility characteristics. Information on the solubility of some lead compounds is given in Sect. 3.2, on physical and chemical properties. Information on additional lead compounds can be found in standard reference texts and is summarized in the IARC (1980) monograph.

4.2.1.1 Inhalation

Human. Prior to the actual absorption of lead by the lungs, some fraction of inhaled airborne lead must be deposited in the respiratory tract. The rate of deposition of particulate airborne lead in adult humans is ~30 to 50% and is modified by factors such as particle size and ventilation rate (EPA 1986a). Relatively little is known about the deposition of airborne lead in children, because of the lack of data on pediatric respiratory aerosol physiology (Hammond 1982). Once deposited in the lower respiratory tract, lead is almost completely absorbed, and all chemical forms of lead also appear to be absorbed (EPA 1986a). Chamberlain et al. (1978) found that 20% of inhaled lead was absorbed within 1 h, and 70% was absorbed within 10 h, in human subjects breathing lead-containing engine exhausts or lead oxide and lead nitrate aerosols at 2-10 $\mu g/m^3$ Pb. Some evidence for complete absorption of lead from the respiratory tract may be the lack of lead found at autopsy in the lung tissues of occupationally exposed lead workers (Barry 1975) and nonoccupationally exposed subjects (Gross et al. 1975).

In human subjects exposed to airborne concentrations of tetraalkyl lead compounds (~1 mg/m^3 breathed through a mouthpiece, 10-40 breaths of ~1-L volume), 37% of inhaled tetraethyl lead and 51% of inhaled tetramethyl lead were initially deposited in the respiratory tract, but a considerable percentage of the lead initially deposited was lost through exhalation of these volatile compounds. Approximately 30 to 40% of the amount of tetraalkyl lead inhaled in vapor is absorbed by the lungs (Heard et al. 1979).

Animal. Inhaled lead is absorbed extensively and rapidly by experimental animals as well as humans (EPA 1986a). Morgan and Holmes (1978) measured absorption rates of 50% within 1 h and 98% within 7 days in adult rats breathing ^{203}Pb-labeled engine exhaust aerosols (6 mg/m^3 Pb). Similar results were obtained in studies with other species (EPA 1986a).

4.2.1.2 Oral

Human. Oral intake of lead can result from consuming lead-containing food and beverages and from swallowing lead deposited in the upper respiratory tract after inhalation exposure (Kehoe 1987). In addition, the ingestion of lead in children may occur through normal mouthing activity and pica (EPA 1986a).

The primary site of lead absorption in children is the gastrointestinal tract (Hammond 1982). For dietary lead, absorption in children is ~50%, compared with 8% (Hammond 1982) or 15% (Chamberlain et al. 1978) gastrointestinal lead absorption measured in adults. The solubility of a particular lead salt in gastric acid (see Sect. 3.2, on physical and chemical properties) and a number of dietary factors (Sect. 4.4, on chemical interactions) will affect the extent and rate of gastrointestinal absorption of lead. Fasting also has a pronounced effect on the gastrointestinal absorption of lead. Absorption can be as high as 45% in adults under fasting conditions (Chamberlain et al. 1978). Based on studies in rats, Barltrop and Meek (1979) found an inverse relationship between lead particle size and gastrointestinal absorption. The extent of gastrointestinal absorption of lead from nonfood sources in children has been estimated from data in animals and chemical parameters to be ~30% from dirt and dust and 17% from paint chips (Drill et al. 1979).

Animal. The extent of absorption of lead in adult experimental animals (1 to 15%) is similar to that measured for adult humans (EPA 1986a). Also similar to findings in humans, the extent of gastrointestinal absorption of lead in experimental animals is age dependent. The rat pup absorbs 40 to 50 times more lead via the diet than does the adult rat (Kostial et al. 1971, 1978; Forbes and Reina 1972). This difference may be due, in part, to dietary differences and to the presence of an undeveloped, selective intestinal barrier to lead in the rat neonate (EPA 1986a). A greater degree of absorption of lead by the gut than by other routes was also noted in nonhuman primates, such as infant and juvenile monkeys (Munro et al. 1975, Pounds et al. 1978). Particle size also influences the degree of gastrointestinal absorption. An inverse relationship was found in rats fed diets containing metallic lead of particle sizes between 0 and 250 microns (Barltrop and Meek 1979).

Specific data regarding the gastrointestinal absorption of alkyl lead compounds were not identified in the available literature. Apparently, tetraethyl lead is absorbed more slowly after oral administration than after dermal application in the rabbit, as evidenced by the rapid onset of toxic symptoms, but dermal absorption was not measured quantitatively (Kehoe 1927). Rhesus monkeys have been shown to absorb tetraethyl lead more readily than tetramethyl lead after ingestion, although specific rates or doses were not reported (Heywood et al. 1979).

4.2.1.3 Dermal

Human. Dermal absorption of inorganic lead compounds is reported to be much less significant than absorption by inhalation or oral routes of exposure, because of the greatly reduced dermal absorption rate (EPA 1986a).

Absorption of lead from ^{203}Pb-labeled lead acetate in cosmetic preparations (0.1 mL of a lotion containing 6 mmol lead acetate/L or 0.1 g of a cream containing 9 mmol lead acetate/kg) applied to the skin for 12 h was measured to be 0 to 0.3% in humans, and was expected to be 0.06% during normal use of such preparations (Moore et al. 1980). Absorption of alkyl lead compounds through the skin has been reported after accidental exposures (Hayakawa 1972, Gething 1975).

Animal. Alkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931, Laug and Kunze 1948). In three rabbits treated with 0.75 mL tetraethyl lead, which was allowed to spread uniformly over an area of 25 cm2 on the abdominal skin, lead was found in the carcass at 10.6 mg after 0.5 h, 2.43 mg after 1 h, and 4.41 mg after 6 h (Kehoe and Thamann 1931). Laug and Kunze (1948) found that tetraethyl lead was absorbed by the skin of rats to a much greater extent than lead oleate, lead acetate, and lead arsenate.

4.2.2 Distribution and Body Burden

Described simply, the body burden of a particular chemical is the total amount of that chemical found in the body. The body burden of lead represents the difference between cumulative lifetime absorption of lead from all sources and total excretion (Landrigan et al. 1985).

Rather than being distributed homogeneously throughout the body, lead is dispersed among several physiologically distinct compartments (Landrigan et al. 1985). A three-compartment model proposed by Rabinowitz et al. (1976), based on tracer and balance data from five healthy men, identifies the relative proportioning of lead between the bone, blood, and soft-tissue pools (Fig. 4.1). The figure shows the lead content and mean half-life of each pool and the rates of lead movement between pools (λ).

This model indicates that the lead content, the mean life (residence time) of lead in each pool, and the rates of movement between pools are different for each compartment. The blood compartment shows the shortest half-life (36 days), followed by the soft-tissue compartment (40 days), and then by the bone compartment (10^4 days or ~27 years). Bone contains most of the total body burden of lead. Further refinement of this three-compartment model is advanced by Marcus (1985a,b,c) and presented in Fig. 4.2.

Once absorbed, inorganic lead is distributed in essentially the same manner regardless of the route of absorption (Hammond 1982). Therefore, the distribution and body burden of absorbed lead can be discussed for human and animal studies without differentiating the route of absorption. The distribution of lead in man has been well characterized.

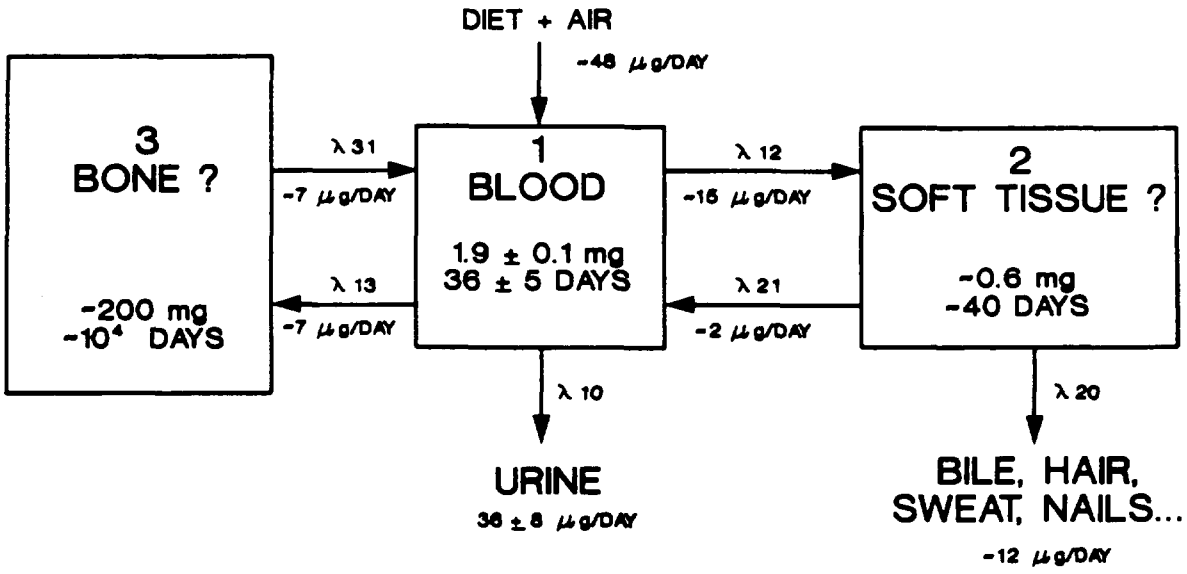


Fig. 4.1. Lead metabolism model. *Source:* Rabinowitz et al. 1976.

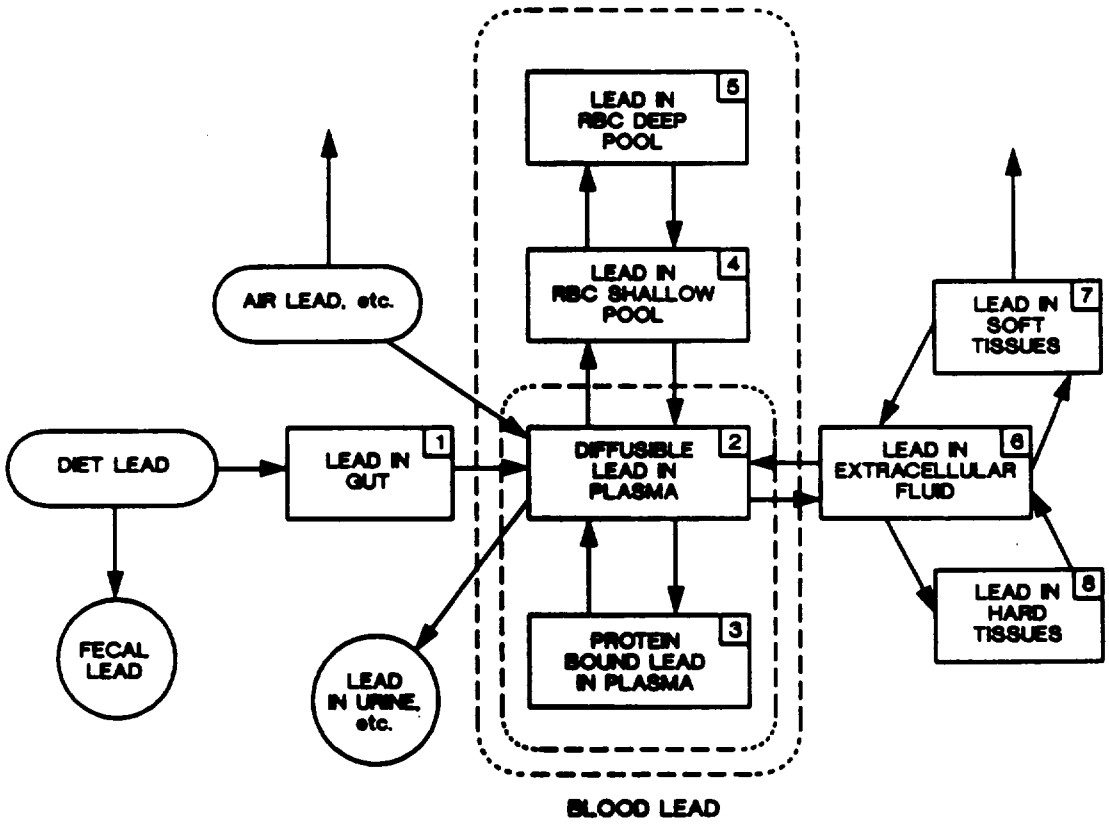


Fig. 4.2. A compartmental model for lead biokinetics, with multiple pool for blood lead. *Source:* Marcus 1985a,b,c.

4.2.2.1 Human

The distribution of lead in the body is initially dependent on the rate of delivery by the bloodstream to various organs and tissues. A subsequent redistribution may then occur, based on the relative affinity of tissues for the element (EPA 1986a). A number of age-related differences in lead distribution and body burden exist between children and adults. These relationships are discussed below.

Lead in blood. Under steady-state conditions, >99% of blood lead is associated with the erythrocytes (Everson and Patterson 1980). Over 50% of this erythrocyte lead pool is bound to hemoglobin, particularly HgA_2, with lesser amounts bound to other proteins (Bruenger et al. 1973). Fetal hemoglobin appears to have a greater affinity for lead than does adult hemoglobin (Ong and Lee 1980).

The relationship between the fractions of lead distributed in the erythrocytes and plasma has been described by Manton and Cook (1984). At blood lead levels ≤40 μg/dL, blood lead and serum lead levels increase linearly in a positive fashion; at higher blood lead levels, they assume a curvilinear relationship (Fig. 4.3). The ratio of lead in serum to that in whole blood increases dramatically at blood lead levels >40 μg/dL. In vitro data of the partitioning of blood lead between erythrocytes and plasma show a positive linear correlation at blood lead levels ≤100 μg/dL and deviation from linearity above that value (Clarkson and Kench 1958). The departure from linearity of this relationship in vivo at blood lead levels >40 μg/dL may be caused by altered cell morphology at high blood lead levels, resulting in a reduced availability or stability of lead binding sites in the erythrocytes (EPA 1986a). The half-life of lead in adult human blood has been measured as 36 days by Rabinowitz et al. (1976) and 28 days by Griffin et al. (1975). The biological half-life of lead in the blood of 2-year-old children was reported to be ~10 months (Succop et al. 1987).

Lead in mineralizing tissue. In human adults, ~95% of the total body burden of lead is found in the bones. In contrast, bone lead accounts for 73% of the body burden in children (Barry 1975, 1981). This large pool of lead in adults can serve to maintain blood lead levels long after periods of exposure have ended (O'Flaherty et al. 1982).

Two physiological compartments appear to exist for lead in bones. In one compartment, bone lead is essentially inert, having a half-life of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of lead between bone and soft tissue or blood (Rabinowitz et al. 1976, 1977). The presence of labile lead may be a more accurate predictor of recent exposure or imminent toxicity than total body or whole blood burdens (EPA 1986a).

Increased mobilization of lead from human bone can occur during the physiological stresses of pregnancy and lactation (ATSDR 1988). Zaric et al. (1987) found that women living in a smelter region had higher blood levels of lead during pregnancy, and Manton (1985) reported increased blood levels of lead in women during lactation.

Bone lead levels are known to increase as a function of age. In men 60 to 70 years old, the total bone lead content may be ≥200 mg, while children <16 years old have been shown to have total skeletal lead

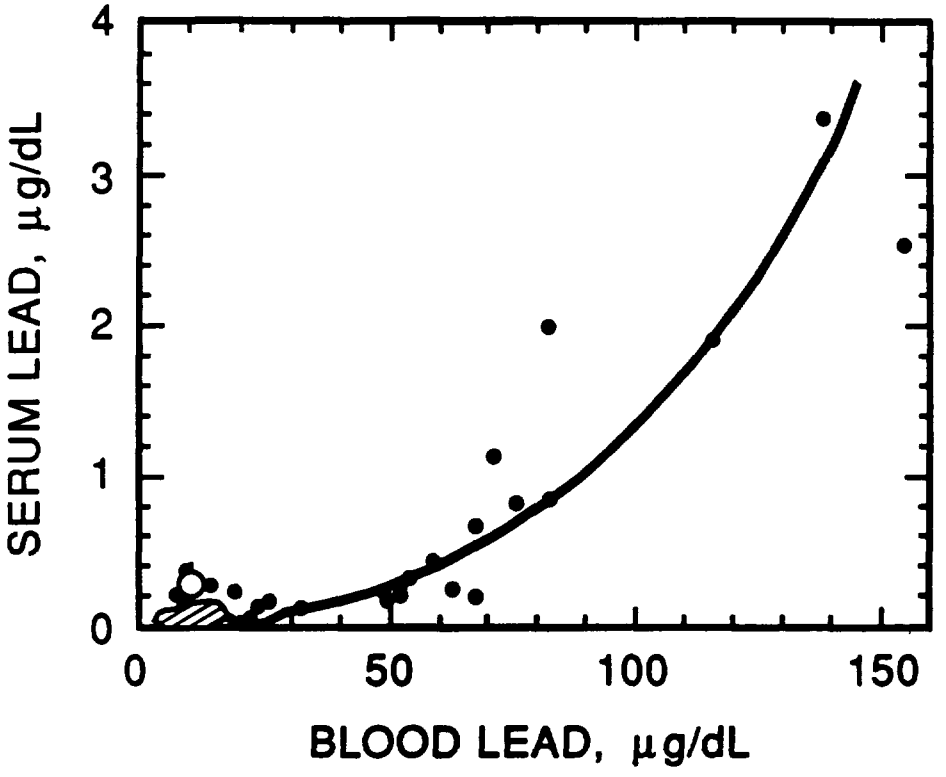


Fig. 4.3. Curvilinear relationship of serum lead to blood lead. Cross-hatched area represents several overlapping points. *Source:* Manton and Cook 1984.

levels of 8 mg (Barry 1975). These data are based on a limited sample size. Drasch et al. (1987) analyzed the bone lead content at autopsy in a total of 240 adults with no known occupational exposure to lead. Each group of 40 subjects represented a different age decade. The results indicated that the lead content of the temporal bone increased steadily with age, whereas the lead content of the mid-femur and that of the pelvic bone reached a plateau in middle age followed by a decline with advancing age. The levels of lead in teeth, especially in the dentin, are also known to increase with age. This age-related increase may occur as a function of exposure (Steenhout and Pourtois 1981), which supports the use of dentin lead measurements as an indicator of exposure (Needleman and Shapiro 1974).

Lead in soft tissues. In most soft tissues, lead does not appear to accumulate as a function of age in humans over 20 years old (Barry 1975, 1981), but these data are based on limited sample size. The exceptions to this trend are the renal cortex, which may retain lead due to the formation of lead nuclear inclusion bodies (Indraprasit et al. 1974), and the aorta, in which entrapped lead may be present in atherosclerotic plaque deposits (Barry 1975, 1981).

Brain tissue does not show an age-related increase in lead accumulation, but increased brain lead levels have been measured in subjects with known or suspected occupational exposure to lead (Barry 1975). Several authors have shown that lead is selectively accumulated in the hippocampus in both children and adults (EPA 1986a).

4.2.2.2 Animal

Cory-Slechta (1987) examined the effects of aging on the tissue distribution of lead acetate. After administration of the compound in drinking water to juvenile (21-day-old), adult (8-month-old), and old (16-month-old) rats for 11 months, age-related increases in distribution were found in the brain, liver, and blood but not in the kidney. An age-related decline was found in the femur. The increased brain and liver concentrations with age may be the result of age-related alterations in absorption, excretion, net deposition in bone, and bone demineralization.

Miller et al. (1983) measured tissue distribution of radiolabeled lead after administering lead acetate by gavage to neonatal rats. One day after administration of the first dose of 50 mg/kg lead acetate, lead had accumulated in the liver, kidney, intestine, and intestinal contents. No lead was found in the blood, bone, or brain. Fifteen days after the first dose, and after the 50-mg/kg dose had been repeated for a total of five administrations, the highest concentration of lead was found in the femur. Brain lead levels had also increased. No accumulation of lead was observed in the lungs, heart, stomach, or spleen over the dosing period.

Hammond (1971) reported high initial lead concentration in soft tissues after administration of a single dose (route unspecified) of lead to rats, followed by rapid excretion and transfer of the lead to bone. Hammond (1982) also reported that the distribution of lead appeared to be independent of route of absorption and corresponded to the three-compartment model of distribution.

4.2.2.3 Pharmacokinetic models

A number of mathematical pharmacokinetic models for lead have been proposed to explain and predict such parameters as intercompartmental lead exchange rates, retention of lead in various pools, and relative rates of distribution among the tissue groups.

An early model by Rabinowitz et al. (1976) described lead kinetics in terms of three compartments: a central blood compartment, a soft tissue compartment, and a bone compartment (see Fig. 4.1). This model predicted half-life durations of increasing length from blood to soft tissue to bone compartments. Bone is calculated to contain most of the total body burden of lead in this model.

The generation of more recent data on lead pharmacokinetics has allowed for a refinement of this three-compartment model. Marcus (1985a,b,c) has proposed a multicompartment kinetic model for lead that addresses the diffusion of lead into bone and such principles as plasma-erythrocyte lead interactions.

For the bone diffusion model, Marcus (1985a) used the lead kinetic parameters generated for the dog. This model, which accounts for the exchange of lead between blood in bone canaliculi and the crystalline bone of the osteon, enables one to predict the effect of a number of parameters (such as diffusion and surface area) on the kinetics of lead in bone.

A similar multicompartment model was developed by Marcus (1985c) to describe the kinetics of lead in plasma and erythrocytes. Based on the data collected by DeSilva (1981), Marcus (1985c) incorporated four blood lead compartments into his model: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool. This relationship is depicted in Fig. 4.2. When this model is applied to the data of DeSilva (1981), a curvilinear relationship results between plasma and blood lead levels. One factor that may account for this nonlinearity is the induction of lead-binding proteins in the erythrocytes as blood lead levels increase (Gonick et al. 1985; Raghaven and Gonick 1977; Raghaven et al. 1980, 1981).

4.2.2.4 Transplacental transfer

Transplacental transfer of lead in humans has been demonstrated in a number of studies, and lead has been identified in umbilical cord blood. In the work of Bellinger et al. (1987a), the mean lead concentration ± SD in umbilical cord blood from a sample size of >11,000 was 6.6 ± 3.2 μg/dL. In a study of 236 mothers and infants in Glasgow, Scotland, the geometric mean blood lead levels were 14 μg/dL for the mothers and 12 μg/dL for the infants (Moore et al. 1982). Fetal uptake of lead occurs by the 12th week of development and increases throughout development, as reported by Barltrop (1969) and Horiuchi et al. (1959). These authors measured the highest lead levels in fetal bone, kidney, and liver tissue, with lesser amounts present in the brain and heart. There is no metabolic barrier to the uptake of lead by the fetus (ATSDR 1988); therefore, exposure of women to lead during pregnancy results in uptake by the fetus. Moreover, as discussed in Sect. 4.2.2.1, in this subsection on distribution of lead in mineralizing tissue of humans, the

physiological stress of pregnancy may result in mobilization of lead from maternal bone, further increasing the uptake of lead by the fetus. Thus, the fetal uptake of lead can occur from a mother who was exposed to lead before pregnancy, even if no lead exposure occurred during pregnancy.

4.2.3 Metabolism

Inorganic lead ion in the body is not known to be "metabolized" or biotransformed per se; primarily, it is absorbed, distributed, and then excreted (Hammond 1982). Conversely, alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450 (Jensen 1984).

Most of the work done to elucidate the mechanism of alkyl lead metabolism has been performed using experimental animals.

4.2.3.1 Human

Relatively few human studies that address the metabolism of alkyl lead compounds were found in the available literature.

In volunteers exposed by inhalation to ^{203}Pb-tetraethyl and -tetramethyl lead, radioactivity was cleared from the blood within 10 h, followed by a reappearance of radioactivity (Heard et al. 1979). The level of radioactivity initially in the plasma was high, indicating that tetraalkyl/trialkyl lead was present. The subsequent rise in blood radioactivity, however, showed that essentially all was present intracellularly, indicating that inorganic or dialkyl lead was present. These results suggest that after the clearance of the tetraalkyl lead from the blood, dealkylation occurred, perhaps in the liver, accounting for the reappearance of radioactivity in the form of inorganic or dialkyl lead in the blood.

The trialkyl lead metabolites of tetraethyl lead and tetramethyl lead have been found in the liver, kidney, and brain following human exposure to the parent tetraalkyl compound; and they have been detected in human brain tissue in individuals with no known occupational exposure to tetraethyl lead or tetramethyl lead (Bolanowska et al. 1967, Nielsen et al. 1978).

4.2.3.2 Animal

The dealkylation, mediated by cytochrome P-450, of alkyl lead compounds is thought to occur in the rat, mouse, and rabbit. This step converts tetraethyl lead and tetramethyl lead to the triethyl and trimethyl metabolites, respectively (EPA 1986a). In addition to oxidative dealkylation, tetraethyl lead may decompose chemically in the gastrointestinal tract, on the skin, or in the tissues (Jensen 1984).

Further biotransformation of these intermediate metabolites is highly species-specific. Rats are not known to convert triethyl lead to the diethyl form (Bolanowska 1968), but significant amounts of diethyl lead are measured in rabbit urine after alkyl lead administration (Arai et al. 1981). Final conversion to inorganic lead may take place, although trialkyl lead compounds are usually stable in biological tissues (Cremer 1965).

4.2.4 Excretion

In man or animals, any dietary lead not absorbed by the gastrointestinal tract is eliminated in the feces. Airborne lead that has been swallowed and not absorbed is eliminated in a similar fashion. The lead that is not retained is either excreted by the kidney or excreted through biliary clearance into the gastrointestinal tract (EPA 1986a).

4.2.4.1 Human

Using the data of Kehoe (1961a,b,c), Rabinowitz et al. (1976), and Chamberlain et al. (1978), Rosen (1985) found that 50 to 60% of the absorbed fraction of lead in adults in a steady-state condition with regard to lead intake/output was excreted on a short-term basis. Chamberlain et al. (1978) found the half-life of this short-term fraction to be 19 days.

From comparison of data on lead kinetics for children and adults, infants apparently have a lower total excretion rate for lead. Young children (infants from birth to 2 years of age) have been shown to retain 34% of the total amount of lead absorbed, based on a study by Ziegler et al. (1978), whereas data by Rabinowitz et al. (1977) demonstrate only a 1% retention of an absorbed dose of lead in adults.

Excretion of alkyl lead compounds in humans has been reported to occur primarily through the feces after inhalation exposure (Machle 1935).

For individuals who are not exposed occupationally to alkyl lead compounds, a normal value for lead in urine is 0.06 mg/L. Moderately exposed workers were shown to have mean levels of lead in urine of 0.09 to 0.15 mg/L (Robinson 1974).

4.2.4.2 Animal

In experimental animals, the relative contribution of the urinary and fecal routes to overall lead excretion is dose and species dependent. In the rat, initial excretion occurs in the urine, followed by greater excretion in the feces (Morgan et al. 1977, Castellino and Aloj 1964, Klaassen and Shoeman 1974). As the dose increases, the proportion of the lead excreted into the gut via bile increases (Klaassen and Shoeman 1974). Biliary excretion of lead by dogs amounted to ~2% of that by rats, and biliary excretion of lead by rabbits amounted to ~50% of that by rats (Klaassen and Shoeman 1974).

Species differences also exist in the rate and extent of total lead excretion. In rats, >50% of orally or parenterally administered lead was excreted in 6 to 14 days (Morgan et al. 1977, Moncilovic and Kostial 1974, Castellino and Aloj 1964, Klaassen and Shoeman 1974). Dogs excreted 52% of injected lead by 21 days, 83% by 1 year, and 87% by 2 years (Lloyd et al. 1975). Adult mice excreted 62% of injected lead by 50 days (Keller and Doherty 1980a), and adult rhesus monkeys excreted 18% in 4 days (Pounds et al. 1978).

In rats, excretion of lead was biphasic, with half-lives of 21 h for the fast phase and 280 h for the slow phase (Morgan et al. 1977).

Dogs excreted lead in three phases, with half-lives of 12, 184, and 4,951 days (Lloyd et al. 1975). The half-life of the terminal phase of a biphasic elimination curve for mice was 110 days (Keller and Doherty 1980a).

Lead can also be excreted in the milk of lactating animals (Keller and Doherty 1980b, Lorenzo et al. 1977, Kostial and Momcilovic 1974).

The renal tract is the main route of lead excretion of various species exposed to alkyl lead compounds (Grandjean and Nielsen 1979). Rabbits given tetraethyl lead parenterally excreted diethyl lead (69%), inorganic lead (27%), and triethyl lead (4%) (Arai et al. 1981).

4.3 TOXICITY

Most of the human dose-effect data for the effects of lead are available in terms of internal exposure levels (i.e., blood lead levels) rather than in terms of external exposure levels. Exposure to lead in occupational studies is primarily through inhalation, although some contribution to body burden is derived from the oral route. Conversely, the general population, including children, is exposed to lead primarily through the oral route, but with some contribution to body burden through inhalation. The human occupational and general population studies are, accordingly, discussed in the subsection corresponding to the primary route of exposure for the study group, but this in no way implies that exposure occurred exclusively by that route.

4.3.1 Lethality and Decreased Longevity

4.3.1.1 Inhalation

Human. Mortality data for workers exposed occupationally to lead have been analyzed (EPA 1986a). Cooper et al. (1985) reported a cohort mortality study of employees at lead-producing facilities. Two cohorts of male lead workers, 4,519 battery plant workers, and 2,300 lead production workers, all of whom had been employed for at least 1 year during 1946 through 1970, were studied for mortality from 1947 through 1980. Overall mortality and standardized mortality ratios were determined. From 1947 through 1972, mean blood lead levels were determined to be 63 μg/dL for 1,326 battery workers and 80 μg/dL for 537 lead production workers. (Blood lead data were not available for many of the workers, and most of the monitoring was done after 1960.) The number of observed deaths from all causes combined was significantly greater ($P < 0.01$) than expected for both groups. The increased mortality rates resulted in large part from malignant neoplasms; chronic renal disease, including hypertension and nephritis; and "ill-defined" causes. It should be noted that this study has been criticized during evaluation of cancer mortality data because of lack of control for potentially confounding exposures to other chemicals and for smoking (EPA 1988a).

Animal. Lethality data for animals exposed to inorganic lead compounds by inhalation were not found in the available literature. The 1-h inhalation LC_{50}s in rats for tetramethyl and tetraethyl lead were reported to be 8,870 and 850 mg/m^3 (Cremer and Callaway 1961).

High rates of mortality were observed in rats exposed to tetramethyl lead for 7 h/day, 5 days/week at 63 mg/m^3 for 10 days, 49 mg/m^3 for 18 days, and 22 mg/m^3 for 35 days (Davis et al. 1963). In rats similarly exposed to tetraethyl lead, high rates of mortality occurred at 46 mg/m^3 for 5 days and 22 mg/m^3 for 14 days. The rats that died from exposure to either chemical died in a comatose state following the development of convulsions. No treatment-related mortality was observed for either chemical at 12 mg/m^3 for up to 150 days.

Dogs exposed to tetramethyl lead for 7 h/day, 5 days/week at ≥12 mg/m^3 died within 15 days; dogs exposed on the same schedule at 4 mg/m^3 died after 84 to 107 exposures (Davis et al. 1963). All dogs similarly exposed to tetraethyl lead at 12 to 42 mg/m^3 died within 30 days. The tetraethyl lead experiment did not include a 4-mg/m^3 group.

4.3.1.2 Oral

Human. In children, entry of lead into the body occurs primarily by ingestion, although inhalation also contributes to body burden. Once lead intoxication has proceeded to encephalopathy, the risk of death exists. Dose-response information on a pediatric population relating blood lead levels with the occurrence of acute encephalopathy and death was compiled by NAS (1972) using data from Chisolm (1962, 1965) and Chisolm and Harrison (1956). The range of blood levels associated with encephalopathy was ~90 to 700 or 800 μg/dL (mean ~330 μg/dL), and the range associated with death was ~125 to 750 μg/dL (mean: 327 μg/dL).

The mortality rate for untreated lead encephalopathy in children was ~65% prior to the introduction of chelation therapy (EPA 1986a). With the advent of chelation therapy, first with BAL (2,3-dimercapto-1-propanol, dimercaprol, British Anti-Lewisite), and shortly thereafter with $CaNa_2EDTA$ (calcium disodium ethylenediaminetetraacetate), mortality was reduced to ~25 to 33%. The introduction of combined BAL-$CaNa_2EDTA$ therapy in 1960 reduced mortality to <5% (Chisolm 1968).

In adults, a direct association between lead level in the aorta and death from heart-related disease was found in a study of 75 autopsies of persons who had resided in a soft-water, leached soil region of North Carolina (Voors et al. 1982). Details of this study are described in Sect. 4.3.2.3 on cardiovascular toxicity, in the subsection on oral exposure in humans.

Animal. Oral LD_{50} values for lead compounds were not found in the available literature. Sax (1984), however, listed LD_{LO} values for a number of lead compounds (Table 4.1). An LD_{LO} is defined as the lowest dose of a substance given over any given period of time in one or more divided portions reported to have caused death (Sax 1984). Furthermore, unlike LD_{50}s, since these values are not derived statistically, comparisons between compounds and species are difficult. Nevertheless, it is apparent that the alkyl lead compounds are substantially more toxic than the inorganic lead compounds.

In a 2-year feeding study, rats were given lead acetate in the diet at lead concentrations of 0, 10, 50, 100, 500, 1,000, or 2,000 ppm (Azar et al. 1973). (This study is described in more detail in Sect. 4.3.2.1 on systemic/target organ toxicity, in the subsection on effects on heme

Table 4.1. Oral LD_{LO} values for lead compounds

Compound	Species	LD_{LO} (mg/kg compound)	LD_{LO} (mg/kg Pb)
Lead acetate	Dog	300	191
Lead chloride	Guinea pig	2,000	1,490
Lead nitrate	Guinea pig	500	313
Lead oxide	Dog	1,400	1,300
Lead sulfate	Dog	2,000	1,366
	Guinea pig	30,000	20,500
Tetraethyl lead	Rat	17	11
	Rabbit	30	19
Tetramethyl lead	Rabbit	24	19

Source: Sax 1984.

synthesis and erythropoiesis in animals after oral exposure.) The percentage mortality, as compared with controls, was slightly increased in males at 500 and 2,000 ppm but not at 1,000 ppm and in females at 1,000 ppm but not 2,000 ppm; statistical analyses were not provided. The authors stated that the reason for these discrepant results was not known. The apparent lack of a dose-response relationship in either sex precludes meaningful conclusions regarding effect levels for mortality in this study.

In a drinking water study, groups of eight young (21 days old), eight adult (8 months old), and eight old (16 months old) male F344 rats were administered 0 or 50 ppm of lead acetate in the drinking water for 11 months (Cory-Slechta 1987). The incidence of mortality in all three treated groups was similar to the incidence in the age-matched control groups: 0/8 treated vs 1/8 control for the young rats, 1/8 treated vs 0/8 control for the adult rats, and 3/8 treated vs 2/8 control for the old rats. Deaths in the old and adult groups were attributed to tumors (tumor type not specified). Blood lead levels in the lead-treated groups at 6 and 11 months of treatment were 14.1 and 8.5 μg/dL in young rats, 25.1 and 15.9 μg/dL in adult rats, and 29.6 and 29.6 μg/dL in old rats. Blood lead levels in the control groups were "negligible" (detection limit 5 μg/dL).

4.3.1.3 Dermal

The only data located regarding lethality of dermally applied lead compounds are LD_{LO}s for alkyl lead compounds in animals. For tetraethyl lead, dermal LD_{LO}s are 830 mg/kg (532 mg/kg Pb) for rabbits and 995 mg/kg (637 mg/kg Pb) for guinea pigs (Sax 1984). For tetramethyl lead, the dermal LD_{LO} is 3,391 mg/kg (2,628 mg/kg Pb) for rabbits (Sax 1984).

4.3.2 Systemic/Target Organ Toxicity

4.3.2.1 Effects on heme biosynthesis and erythropoiesis

The process of heme biosynthesis is outlined in Fig. 4.4. Lead interferes with heme biosynthesis by altering the activity of three enzymes: delta-aminolevulinic acid synthetase (ALA-S), delta-aminolevulinic acid dehydrase (ALA-D), and ferrochelatase. Lead indirectly stimulates the mitochondrial enzyme ALA-S, which catalyzes the condensation of glycine and succinyl-coenzyme A to form delta-aminolevulinic acid (ALA). The activity of ALA-S is the rate-limiting step in heme biosynthesis; increase of ALA-S activity occurs through feedback derepression. Lead directly inhibits the cytosolic enzyme ALA-D, which catalyzes the condensation of two units of ALA to form porphobilinogen. Inhibition of ALA-D and feedback derepression of ALA-S result in accumulation of ALA. Lead decreases the activity of the mitochondrial enzyme ferrochelatase, which catalyzes the insertion of iron (II) into the protoporphyrin ring to form heme. The action of lead on this enzyme occurs either by direct inhibition or by alteration of intramitochondrial transport of iron (EPA 1986a, Moore and Goldberg 1985).

Lead inhibition of ferrochelatase results in an accumulation of protoporphyrin IX, which is present in the circulating erythrocytes as

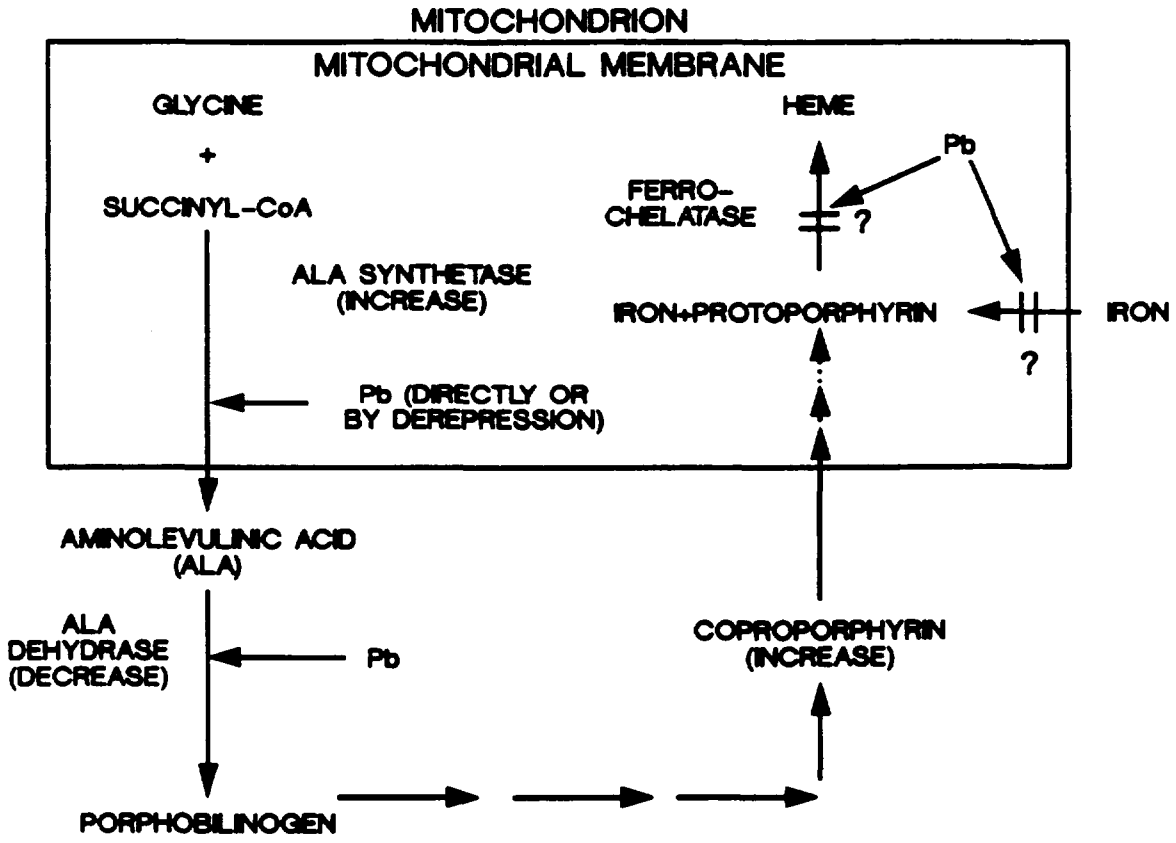


Fig. 4.4. Effects of lead on heme biosynthesis. *Source:* EPA 1986a.

zinc protoporphyrin (ZPP), due to the placement of zinc, rather than iron, in the porphyrin moiety. ZPP is bound in the heme pockets of hemoglobin and remains there throughout the life of the erythrocyte. Assays used in studies of protoporphyrin accumulation measure ZPP or total erythrocyte protoporphyrin (EP) [also called free erythrocyte protoporphyrin (FEP), because ZPP is converted to this form during extraction]. Because accumulation of ZPP occurs only in erthrocytes formed during the presence of lead in erythropoietic tissue, this effect will be detectable in circulating erythrocytes only after a lag time reflecting maturation of erythrocytes and will not reach steady state until the entire population of erythrocytes has turned over, in ~120 days (EPA 1986a, Moore and Goldberg 1985).

A marked interference with heme synthesis results in a reduction of the hemoglobin concentration in blood. Decreased hemoglobin production, coupled with an increase in erythrocyte destruction, results in a hypochromic, normocytic anemia with associated reticulocytosis. Decreased hemoglobin and anemia have been observed in lead workers and in children with prolonged exposure at higher blood lead levels than those noted as threshold levels for inhibition or stimulation of enzyme activities involved in heme synthesis (EPA 1986a).

The increase in erythrocyte destruction may be due in part to inhibition by lead of pyrimidine-5'-nucleotidase, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte. This enzyme inhibition and nucleotide accumulation affect erythrocyte membrane stability and survival by alteration of cellular energetics (Angle et al. 1982, EPA 1986a).

Inhalation, human. One experimental study of the effects of inhalation exposure to lead on heme synthesis in humans was available. In this study (Griffin et al. 1975), adult male volunteers were exposed to particulate lead at 3.2 or 10.9 $\mu g/m^3$ Pb in air for 23 h/day for 3 to 4 months. Mean blood lead levels increased from 20 $\mu g/dL$ (preexposure) to 27 $\mu g/dL$ at the 3.2-$\mu g/m^3$ exposure level and from 20 $\mu g/dL$ (preexposure) to 37 $\mu g/dL$ at the 10.9-$\mu g/m^3$ exposure level. ALA-D decreased to ~80% of preexposure values in the 3.2-$\mu g/m^3$ group after 5 weeks of exposure and to ~53% of preexposure values in the 10.9-$\mu g/m^3$ group after 4 weeks of exposure. Increases in ALA-S activity have been observed in lead workers (Takaku et al. 1973, Campbell et al. 1977, Meredith et al. 1978). Leukocyte ALA-S was stimulated at a blood lead level of 40 $\mu g/dL$ (Meredith et al. 1978), a level at which ALA-D activity is already significantly inhibited. ALA-D activity correlated inversely with blood lead levels in occupationally exposed individuals (Alessio et al. 1976, Wada et al. 1973, Secchi et al. 1974), as has been seen in subjects with no occupational exposure (see the subsection "Oral, human," below). Secchi et al. (1974) found that erythrocyte ALA-D and hepatic ALA-D activities were correlated directly with each other and correlated inversely with blood lead levels in the range of 12 to 56 $\mu g/dL$.

Inhibition of ALA-D and stimulation of ALA-S result in increased levels of ALA in blood or plasma and in urine. The results of the Meredith et al. (1978) study on lead workers and controls indicated an

exponential relationship between blood lead and blood ALA which extended through the lowest blood lead level, 18 μg/dL. Numerous studies reported direct correlations between blood lead level and log urinary ALA in workers (EPA 1986a), and some of these studies indicated that correlations can be seen at blood lead levels below 40 μg/dL (Selander and Cramer 1970, Lauwerys et al. 1974, Tsuchiya et al. 1978), although the slope may be different (less steep) than at blood lead levels >40 μg/dL.

The elevation of erythrocyte EP or ZPP in lead workers has been documented extensively (EPA 1986a). In its evaluation of the available data, the EPA (1986a) concluded that correlations between blood lead levels and log EP or ZPP indicate an apparent threshold for EP elevation in male workers at 25 to 30 μg/dL (Roels et al. 1975, Joselow and Flores 1977, Grandjean and Lintrup 1978, Odone et al. 1979, Herber 1980). The threshold for EP elevation appears to be somewhat lower (15 to 20 μg/dL) (EPA 1986a) in women than in men (Stuik 1974; Roels et al. 1975, 1976, 1979; Toriumi and Kawai 1981), regardless of whether exposure is primarily by inhalation (occupational) or oral (nonoccupational). These studies were controlled for possible confounding factors such as iron deficiency or age, both of which increase the erythrocyte ZPP.

An increase in urinary coproporphyrin has long been recognized in workers with lead poisoning and used as an indicator of excessive exposure to lead (EPA 1986a). The EPA (1986a) identified a lowest-observed-effect level (LOEL) for elevated coproporphyrin at a blood lead level of 40 μg/dL, but did not present the basis for this conclusion.

The EPA (1986a) concluded that the threshold for a decrease in hemoglobin in occupationally exposed adults is a blood lead level of 50 μg/dL, based on evaluations of the data of Tola et al. (1973), Grandjean (1979), Lilis et al. (1978), Wada et al. (1973), and Baker et al. (1979). The LOEL for frank anemia in adults was reported by the EPA (1986a) as a blood lead level of 80 μg/dL, apparently based on data from the same studies.

Erythrocyte pyrimidine-5'-nucleotidase activity is inhibited in lead workers, with the greatest inhibition and marked accumulations of pyrimidine nucleotides apparent in workers with overt intoxication, including anemia (Paglia et al. 1975, 1977). Pyrimidine-5'-nucleotidase activity was correlated inversely with blood lead when corrected for an enhanced population of young cells due to hemolytic anemia in some of the workers (Buc and Kaplan 1978). Based (apparently) on the data of Paglia et al. (1975) and Buc and Kaplan (1978), the EPA (1986a) concluded that adults tend to show a threshold for inhibition of pyrimidine-5'-nucleotidase at a blood lead level of ≥44 μg/dL.

Inhalation exposure to alkyl lead through chronic sniffing of leaded gasoline occurs in disadvantaged children residing in rural or remote areas of Canada (Boeckx et al. 1977) and in rural American Indian communities in the Southwest (Kaufman 1973). Alkyl lead compounds can be metabolized not only to neurotoxic trialkyl lead metabolites, but also, through further dealkylation, to inorganic lead. In one group of 43 children who all sniffed gasoline, mean blood ALA-D activity was depressed to only 30% of that in controls and there was a significant inverse correlation between ALA-D activity and frequency of sniffing

(Boeckx et al. 1977). Two children with acute lead poisoning associated with gasoline sniffing had markedly lowered hemoglobin levels and elevated urinary ALA and coproporphyrin excretion (Boeckx et al. 1977). Increased urinary lead levels measured during chelation therapy indicated that significant inorganic lead was present.

Inhalation, animal. Pertinent data regarding the effects of inhalation exposure on heme synthesis and erythropoiesis in animals were not located in the available literature.

Oral, human. Two experimental studies of the effects of oral exposure to lead on heme synthesis in humans were available. Two groups of five women and one group of five men who ingested lead acetate at 20 μg/kg/day Pb every day for 21 days experienced decreases in erythrocyte ALA-D by day 3 of lead ingestion (Stuik 1974). The decreases became maximal by day 14 and then remained constant through day 21. An increase in EP occurred in the women, but not in the men, starting after 2 weeks of ingestion. Blood lead levels were ~15 μg/dL before exposure and increased to ~40 μg/dL during exposure. Increased EP was observed in five men at a higher dosage, 30 μg/kg/day Pb (which produced a mean blood lead level of 46 μg/dL), starting after 2 weeks of lead ingestion (Stuik 1974). Similar results were reported by Cools et al. (1976) for 11 men ingesting lead acetate at an initial dosage of 30 μg/kg/day Pb, which was decreased to 20 μg/kg/day Pb or less as necessary to maintain a blood lead level of 40 μg/dL; the mean pre-exposure blood lead level was 17.2 μg/dL.

General population studies indicate that the activity of ALA-D is inhibited at very low blood lead levels, with no threshold yet apparent. Hernberg and Nikkanen (1970) found that ALA-D activity was inversely correlated with blood lead levels over the entire range of 3 to 34 μg/dL in urban subjects never exposed occupationally. Other reports have confirmed the correlation and apparent lack of threshold in different age groups and exposure categories [children, oral--Chisholm et al. (1985), Roels et al. (1976); adults, inhalation--see the subsection "Inhalation, human," above). As described in Sect. 4.3.3 on developmental toxicity, Lauwerys et al. (1978) reported inverse correlations between blood lead levels and ALA-D activity in mothers (at delivery) and their newborns (cord blood). Blood lead levels ranged from ~3 to 30 μg/dL.

Correlations between blood lead levels and urinary ALA similar to those observed in occupationally exposed adults (see the subsection "Inhalation, human," above) have also been reported in children [data of J.J. Chisolm, Jr., reported by NAS (1972)]. A significant linear correlation between blood lead level and log ALA was obtained for data in children 1 to 5 years old with blood lead levels of 25 to 75 μg/dL. The correlation was seen primarily at blood lead levels >40 μg/dL, but some correlation may persist at <40 μg/dL.

Many studies have reported the elevation of erythrocyte EP or ZPP as exponentially correlated with blood lead levels in children (EPA 1986a). The threshold for this effect in children is ~15 μg/dL (Roels et al. 1976; Piomelli et al. 1977, 1982; Rabinowitz et al. 1986; Hammond et al. 1985) and may be lower in the presence of iron deficiency (Mahaffey and Annest 1986, Marcus and Schwartz 1987).

An increase in urinary coproporphyrin is known to occur in children with lead poisoning and has been used diagnostically (EPA 1986a). The EPA (1986a) reported a LOEL for this effect in children at 35 μg/dL, but did not present the basis for this conclusion.

The blood lead threshold for decreased hemoglobin levels in children is judged to be ~40 μg/dL (WHO 1977, EPA 1986a), based on the data of Adebonojo (1974), Rosen et al. (1974), Betts et al. (1973), and Pueschel et al. (1972), and that for frank anemia in children is 70 μg/dL (EPA 1986a), apparently based on data from the same studies. These thresholds are somewhat lower than the corresponding thresholds in occupationally exposed adults (see the subsection "Inhalation, human," above).

Erythrocyte pyrimidine-5'-nucleotidase is inhibited in children at very low blood lead levels. A significant negative linear correlation between pyrimidine-5'-nucleotidase and blood lead level was seen in 21 children with blood lead levels ranging from 7 to 80 μg/dL (Angle and McIntire 1978). Similar results were seen in another study with 42 children whose blood lead levels ranged from <10 to 72 μg/dL (Angle et al. 1982). Additional findings included a direct correlation between cytidine phosphate levels and blood lead levels (log-log). There was no indication of a threshold for these effects of lead in these two studies.

In children, exposure to lead has been shown to inhibit formation of the heme-containing protein cytochrome P-450, as reflected in decreased activity of hepatic mixed-function oxygenases (Alvares et al. 1975, Saenger et al. 1984). Alvarez et al. (1975) reported that children with clinical manifestations of acute lead poisoning did not metabolize the test drug antipyrine as rapidly as did controls. Saenger et al. (1984) reported a significantly reduced 6 beta-hydroxylation of cortisol in children who had positive $CaNa_2EDTA$ tests as compared with a negative, age-matched test group, controlling for free cortisol. These reactions are mediated by hepatic mixed-function oxygenases.

Oral, animal. Dose (blood lead)-effect information for heme synthesis and hematological effects is available in a study by Azar et al. (1973), in which groups of rats (controls--100/sex; treated--50/sex/dose) and dogs (4/sex/dose) were fed lead acetate in the diet at 0, 10, 50, 100, or 500 ppm lead and additional groups of rats (20/sex/dose) were fed 0, 1,000, or 2,000 ppm lead in the same manner for 2 years. In rats, lead produced no effects at 10 ppm (blood lead level = 11.0 μg/dL; not elevated above controls), significant inhibition of ALA-D at ≥50 ppm (blood lead level ≥18.5 μg/dL), significant increase in urinary ALA at ≥500 ppm (blood lead level ≥77.8 μg/dL), and slight but significant decreases in hemoglobin concentration and hematocrit at ≥1,000 ppm (blood lead level ≥98.6 μg/dL). In dogs, lead produced no effects at ≤50 ppm (blood lead level ≤31.5 μg/dL), significant inhibition of ALA-D at ≥100 ppm (blood lead level ≥42.5 μg/dL), and no effect on urinary ALA, hemoglobin, or hematocrit at any exposure level (highest level, 500 ppm, blood lead level = 75.8 μg/dL). Control blood lead levels were 12.7 and 16.4 μg/dL in the two rat groups and 15.8 μg/dL in the dog. Another end point from this study,

carcinogenicity, and blood lead data for all groups are presented in Sect. 4.3.6, carcinogenicity.

Studies in animals indicate that the effects of lead on heme synthesis occur in many tissues. Oral exposure of rats to lead decreased liver ALA-S activity (Silbergeld et al. 1982) increased spleen ALA-S activity (Silbergeld et al. 1982), decreased kidney ALA-S activity (Fowler et al. 1980), decreased brain (Gerber et al. 1978), liver, and spleen (Silbergeld et al. 1982) ALA-D activity, and decreased kidney ferrochelatase activity along with mitochondrial injury and disturbance of function (Fowler et al. 1980).

Formation of the heme-containing cytochromes is inhibited in animals treated intraperitoneally or orally with lead compounds. Goldberg et al. (1978) found an inverse dose-effect relationship between lead exposure and P-450 content of hepatic microsomes and also activity of microsomal mixed-function oxygenases. Meredith and Moore (1979) demonstrated that increasing duration of exposure was associated with decreasing microsomal P-450 content and decreasing microsomal heme content. In addition, delays in the synthesis of the respiratory chain hemoprotein cytochrome C have been noted during administration of lead to neonatal rats (Bull et al. 1979).

Dermal. Pertinent data regarding the effects of dermal exposure to lead on heme synthesis or erythropoiesis in humans or animals were not located in the available literature.

General discussion. The impairment of heme synthesis by lead has a far-ranging impact not limited to the hematopoietic system. The EPA (1986a) summarized the known and potential consequences of the reduction of heme synthesis as shown in Fig. 4.5. One of these consequences, the decrease in cytochrome P-450 content and related enzyme activities in many tissues, is summarized above. Other consequences are discussed in sections to follow.

Effects on some steps in the heme synthesis pathway occur at very low exposure levels, but there is some controversy as to the toxicological significance of a depression in ALA-D activity in the absence of a detectable effect on hemoglobin levels. The EPA (1986a) and ATSDR (1988) are concerned about effects on the heme synthesis pathway, however, because of the emerging evidence of a constellation of effects, including inhibition of ALA-D and pyrimidine-5'-nucleotidase activities; elevations in EP levels; reductions in serum 1,25-dihydroxyvitamin D levels; and subtle neurobehavioral, electrophysiological, growth, and blood pressure effects at low blood lead levels (10-15 μg/d and possibly lower).

4.3.2.2 Neurobehavioral toxicity

Inhalation, human. Studies of occupationally exposed populations are the main source of data for lead toxicity to adults. In these studies, exposure was primarily by inhalation, but with an oral component as well. Dose-response data were available in terms of blood lead levels, rather than external exposure levels.

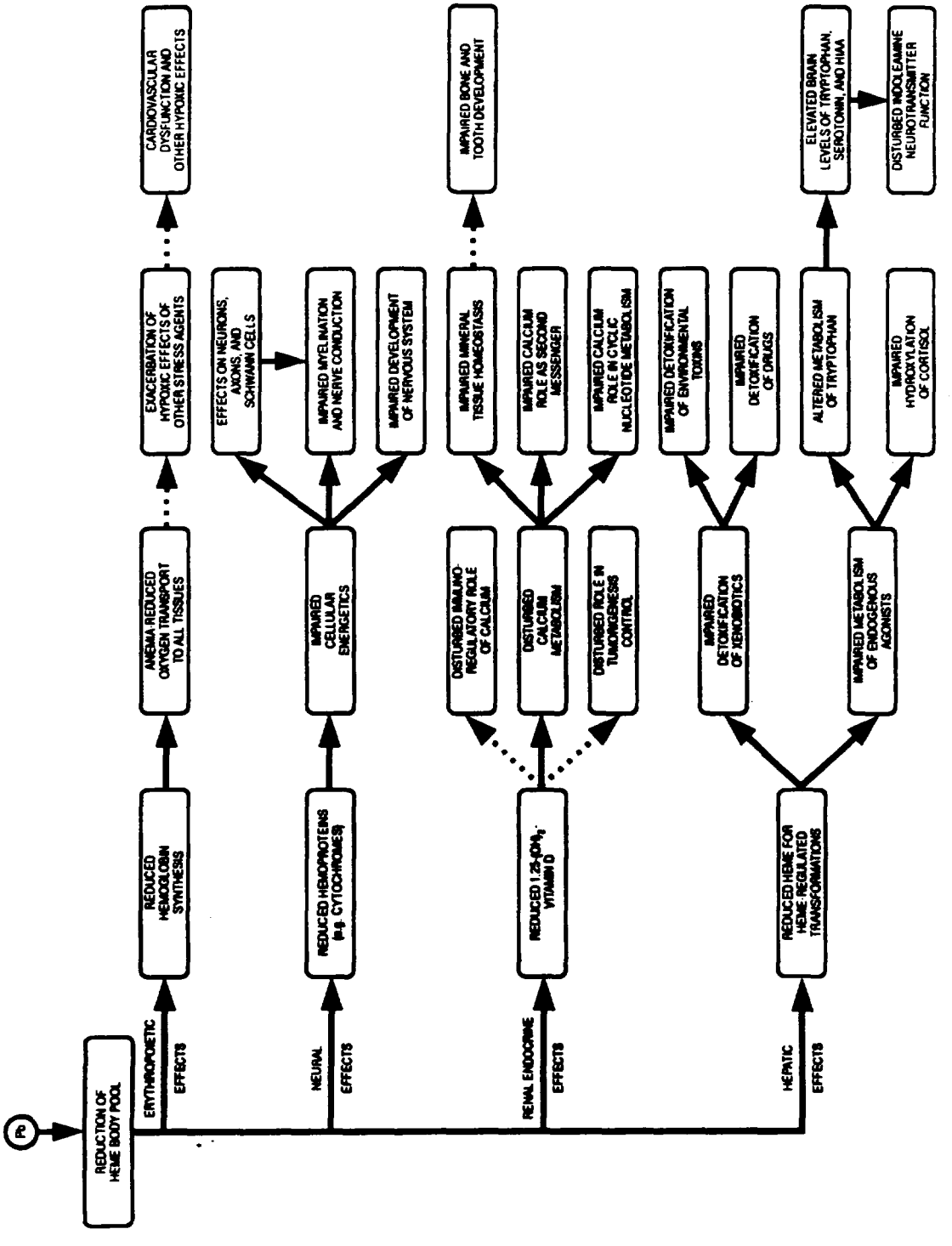


Fig. 4.5. Multiorgan impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead results in disruption of a wide variety of important physiological processes. *Source:* EPA 1986a.

The most severe neurobehavioral effect of lead in adults is lead encephalopathy. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death (Aub et al. 1926, Cantarow and Trumper 1944, Cumings 1959, Teisinger and Styblova 1961). Histopathological findings in fatal cases of lead encephalopathy in adults are similar to those in children [see Sect. 4.3.2.2 on oral (human) exposure].

Severe lead encephalopathy is generally not observed in adults except at blood lead levels well in excess of 120 μg/dL (Kehoe 1961a,b,c). Other data (Smith et al. 1938) suggest that acute lead poisoning, including severe gastrointestinal symptoms and/or signs of encephalopathy, can occur in some adults at blood lead levels of ~100 μg/dL, but the data are somewhat ambiguous.

Evidence of overt neurotoxicity at lower exposure levels is provided in the studies of Haenninen et al. (1979), Baker et al. (1979), and Zimmermann-Tansella et al. (1983). Haenninen et al. (1979) reported significantly increased central and peripheral nervous system and gastrointestinal symptoms among 25 lead workers with maximum blood lead levels of 50 to 69 μg/dL and significantly increased CNS symptoms among 20 lead workers with maximum blood lead levels <50 μg/dL. Referent controls (N = 23) had average blood lead levels of 11.9. Baker et al. (1979) reported that no smelter workers with blood lead levels <40 μg/dL had signs or symptoms of lead intoxication, and 13% of smelter workers with blood lead levels of 40 to 79 μg/dL had extensor muscle weakness or gastrointestinal symptoms. In addition, 5% of the workers with 40 to 59 μg/dL blood lead levels, 14% with 60 to 79 μg/dL, and 36% with >80 μg/dL had anemia.

A study comparing 288 lead-exposed workers (current or historical blood lead >35 μg/dL) at three battery plants with 181 unexposed workers (current blood lead level ≤35 μg/dL) at a truck frame plant reported a few differences in neurobehavioral or psychosocial indices (Parkinson et al. 1986). Because the lead-exposed workers were younger, less educated, employed for fewer years, and earned less income than the unexposed workers, the analysis adjusted for age, education, and income. Exposed workers had mean current, time-weighted-average, and peak blood lead levels of 40.0, 48.8, and 78.8 μg/dL, respectively. Blood lead data for unexposed workers were not characterized in this manner. Exposed workers had an increase in the number of work-related accidents and poorer performance in a motor speed/manual dexterity test with the nondominant hand, and greater levels of conflict in interpersonal relationships as compared with unexposed workers. When multiple regression analyses were performed on the data for exposed workers, only the levels-of-conflict measure showed a significant dose-response relationship with current or cumulative blood lead levels.

Zimmerman-Tansella et al. (1983) and Campara et al. (1984) studied 20 unexposed men (mean blood lead level: 20.4 μg/dL), 20 men exposed to low-lead levels (mean blood lead level: 31.7 μg/dL; range: 26 to 35 μg/dL) and 20 men exposed to high-lead levels (mean blood lead level: 52.5 μg/dL; range: 45 to 60 μg/dL) at an electric storage battery plant.

Consistent and significant dose-response trends were observed in symptoms such as loss of appetite, paresthesis in lower limbs, weakness of upper limbs, and dropping of objects, with the most marked increases in neurological symptoms in the high-lead group (Zimmerman-Tansella et al. 1983). In addition, the high-lead workers performed significantly less well on neurobehavioral tests, with general performance on cognitive and visual-motor coordination tasks and verbal reasoning ability most markedly impaired (Campara et al. 1984).

Taken together, the results of these studies of neurological signs and symptoms at lower exposure levels indicate that the lowest-observed-effect levels for overt signs and symptoms of neurotoxicity in adults is in the range of 40 to 60 μg/dL and that these neurological signs and symptoms occur at roughly the same blood lead levels as do other overt signs and symptoms of lead intoxication, such as gastrointestinal complaints (EPA 1986a).

Neurobehavioral testing has revealed effects in adults at blood lead levels of ~30 μg/dL or more. Disturbances in oculomotor function (saccadic eye movements) in lead workers with mean blood lead levels of 57 to 61 μg/dL were reported in a study by Baloh et al. (1979) with follow-up by Spivey et al. (1980) and in a study by Glickman et al. (1984). Morgan and Repko (1974) reported deficits in hand-eye coordination and reaction time in 190 lead-exposed workers (mean blood lead levels: 60.5 μg/dL). Most of the workers had been exposed between 5 and 20 years. A similar study by Milburn et al. (1976), however, reported no differences between control and lead-exposed workers on neurobehavioral tests. Disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, or coping ability were observed in lead workers with blood lead levels of 50 to 80 μg/dL (Arnvig et al. 1980, Grandjean et al. 1978, Haenninen et al. 1978, Hogstedt et al. 1983, Mantere et al. 1982, Valcuikas et al. 1978). As previously noted, Campara et al. (1984) found that workers with blood lead levels of 45 to 60 μg/dL performed less well on neurobehavioral tests. Hogstedt et al. (1983) found impaired memory and learning ability in workers with time-weighted average blood lead levels of 27 to 52 μg/dL. Baker et al. (1983) observed impaired verbal concept formation, memory, and visual/motor performance and increased rates of depression, confusion, anger, fatigue, and tension among workers with blood lead levels >40 μg/dL.

The EPA (1986a) reviewed and evaluated 28 studies of peripheral nerve function that measured the conduction velocity of electrically stimulated nerves in the arm or leg of lead workers. Particularly noteworthy studies will be summarized here. In prospective occupational studies, Seppalainen et al. (1983) found decreased nerve conduction velocities (NCVs) in workers with blood lead levels of 30 to 48 μg/dL, whereas Spivey et al. (1980) found no significant differences in NCVs in workers with blood lead levels of 60 to 80 μg/dL, relative to controls. Effects in the study of Seppalainen et al. (1983) were seen in the median (motor and sensory) and ulnar (motor and sensory) nerves of ~11 high-exposure workers after 1 or 2 years of exposure. Spivey et al. (1980) tested ulnar (motor and slow fiber) and peroneal (motor) nerves in 55 workers exposed ≥1 year.

In cross-sectional occupational studies, Rosen et al. (1983) observed significant decreases in NCVs in fibular (motor) and sural (sensory) nerves as a function of blood lead levels with duration of exposure showing no effect, and Triebig et al. (1984) reported that decreases in NCVs of ulnar (sensory, distal) and median (motor) nerves were seen primarily at blood lead levels >70 μg/dL. Duration of exposure and number of lead-exposed workers in these two studies were 0.5 to 28 years and 15 workers (Rosen et al. 1983), and 1 to 28 years and 133 workers (Triebig et al. 1984). That the decrease in NCV is due to lead is indicated by the study of Araki et al. (1980), in which median (motor) NCVs in workers with mean blood lead levels of 52 μg/dL were improved significantly when blood lead levels were lowered through $CaNa_2EDTA$ chelation therapy.

The EPA (1986a) concluded that these studies, and the database as a whole, indicate that NCV effects occur in adults at blood lead levels <70 μg/dL, and possibly as low as 30 μg/dL. Ehle (1986), in reviewing many of the studies of NCV effects considered by the EPA (1986a), concluded that a mild slowing of certain motor and sensory NCVs may occur at blood lead levels below 60 μg/dL, but that the majority of studies did not find correlations between blood lead and NCV below 70μg/dL and that slowing of NCV is neither a clinical nor a subclinical manifestation of lead neuropathy in humans. Ehle (1986), however, did not cite or analyze the studies by Rosen et al. (1983) or Seppaleinen et al. (1983). Other reviewers have pointed out that decreases in NCV are slight in peripheral neuropathies (such as that induced by lead) that involve axonal degeneration (Le Quesne 1987), and that although changes in conduction velocity usually indicate neurotoxicity, considerable nerve damage can occur without an effect on conduction velocity (Anderson 1987). The EPA (1986a) noted that although many of the observed changes in NCV may fall within the range of normal variation, the effects represent departures from normal neurological functioning. NCV effects are seen consistently across studies, and, although the effects may not be clinically significant for an individual, they are significant when viewed on a population basis.

Inhalation, animal. Pertinent data regarding the neurobehavioral toxicity of inhaled (inorganic) lead to animals were not located in the available literature.

A study of the organolead compounds tetramethyl and tetraethyl lead reported CNS effects in rats exposed to 12 to 63 mg/m^3 tetramethyl lead or 12 to 46 mg/m^3 tetraethyl lead for 7 h/day, 5 days/week (Davis et al. 1963). Irritable, uncoordinated, and combative behaviors were early signs of toxicity at all exposure levels. Convulsions, coma, and death occurred within 5 to 35 days at all exposure levels but the lowest (i.e., at ≥22 mg/m^3). Animals that died and those sacrificed after 150 days had lesions in the brain and spinal cord. Dogs exposed in a similar manner, but to lower levels of these compounds, died even at the lowest level tested, 4 mg/m^3, after 84 or 107 exposures, and had brain lesions.

Oral, human. In children, entry of lead into the body occurs primarily by ingestion, although inhalation also contributes to body burden. The available dose-response information is expressed in terms of blood lead level rather than external exposure level.

High-level exposure to lead produces encephalopathy in children. According to the EPA (1986a), the most extensive compilation of dose-response information on a pediatric population is the summarization by the NAS (1972) of data from Chisolm (1962, 1965) and Chisolm and Harrison (1956). This compilation relates the occurrence of acute encephalopathy and death in children to blood lead levels determined by the Baltimore City Health Department between 1930 and 1970. Other signs of acute lead poisoning and blood lead levels formerly regarded as asymptomatic were also summarized. An absence of signs or symptoms was observed in some children at blood lead levels of 60 to 300 μg/dL (mean: 105 μg/dL). Acute lead poisoning symptoms other than signs of encephalopathy were observed at blood lead levels of ~60 to 450 μg/dL (mean: 178 μg/dL). Signs of encephalopathy (hyperirritability, ataxia, convulsions, stupor, and coma) were associated with blood lead levels of ~90 to 700 or 800 μg/dL (mean: ~330 μg/dL). The distribution of blood lead levels associated with death (mean: 327) was virtually the same as for levels associated with encephalopathy.

Additional evidence from medical reports (Gant 1938, Smith et al. 1938, Bradley et al. 1956, Bradley and Baumgartner 1958, Cumings 1959, Rummo et al. 1979) suggests that acute encephalopathy in the most susceptible children may be associated with blood lead levels in the range of 80 of 100 μg/dL (EPA 1986a). These latter reports were evaluated in detail by the EPA (1977).

Histopathological findings in fatal cases of lead encephalopathy in children include cerebral edema, altered capillaries, and perivascular glial proliferation. Neuronal damage is variable and may be caused by anoxia (EPA 1986a).

According to the EPA (1986a), numerous studies clearly show that childhood lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Additional studies indicate that children with symptomatic lead poisoning without encephalopathy (blood lead levels >80 to 100) also have an increased incidence of lasting neurological and behavioral impairments (EPA 1986a).

The EPA (1986a) reviewed a number of studies of asymptomatic children with relatively high lead body burdens; these children were identified through lead screening programs or other large-scale programs focusing on mother-infant health relationships and early childhood development. Studies that were conducted rigorously enough to warrant consideration of their findings were those of de la Burde and Choate (1972, 1975), Rummo (1974), Rummo et al. (1979), Kotok (1972), Kotok et al. (1977), Perino and Ernhart (1974), and Ernhart et al. (1981). These studies found that, in general, high-risk lead exposure groups performed less well on IQ or other psychometric tests than did referent control groups with lower lead exposures. Some of these studies did not control for important confounding variables, such as parental IQ or educational background, or, when reanalyzed taking these variables into account, found that differences between lead-exposed and control children were reduced or lost statistical significance. In addition, many of the referent control groups tended to have what are now recognized to be elevated blood lead levels (averaging 20 to 40 μg/dL). Nevertheless, the

EPA (1986a) concluded that the consistent pattern of lower IQ values and other neuropsychologic deficits among the higher lead exposure children in these studies indicate that cognitive deficits occur in apparently asymptomatic children with markedly elevated blood lead levels (starting at 40 to 60 μg/dL and ranging up to ≥70 to 80 μg/dL).

The EPA (1986a) concluded that the average decrements of ~5 IQ points observed in studies by de la Burde and Choate (1972), Rummo (1974), and Rummo et al. (1979), described in more detail below, represent a reasonable estimate of the magnitude of full-scale IQ decrements associated with markedly elevated blood lead levels (mean ~50 to 70 μg/dL) in asymptomatic children.

De la Burde and Choate (1972) found a mean Stanford-Binet IQ decrement of 5 points, fine motor dysfunction, and altered behavioral profiles in 70 preschool children exhibiting pica for paint and plaster and elevated blood lead levels (>30 μg/dL, mean: 58 μg/dL), as compared with results for matched control subjects not engaging in pica for paint and plaster. A follow-up study on these children at 7 to 8 years of age (de la Burde and Choate 1975) reported a mean WISC Full Scale IQ decrement of 3 points and impairment in learning and behavior, despite decreases in blood lead levels since the original study.

Rummo (1974) and Rummo et al. (1979) observed hyperactivity and a decrement of ~16 IQ points on the McCarthy General Cognitive Index (GCI) among children who had previously had encephalopathy and whose mean blood lead levels at the time of encephalopathy were 88 μg/dL. Asymptomatic children with long-term lead exposures and mean blood lead levels of 68 μg/dL had an average decrement of 5 IQ points on the McCarthy GCI, and their scores on several McCarthy Subscales were generally lower than those for controls, but were not significantly different statistically (at $P < 0.05$), while children with short-term exposure and blood lead levels of 60 μg/dL did not differ from controls. Blood lead levels in controls did not exceed 40 μg/dL (mean 23 μg/dL).

A number of general population studies reviewed by the EPA (1986a) evaluated asymptomatic children with lower lead body burdens than those evaluated in the above studies. Some of these studies provide evidence of an association between neurobehavioral effects and the relatively low body burdens representative of general pediatric populations. A study of 158 first- and second-grade children by Needleman et al. (1979) provides acceptable evidence for the association of full-scale IQ deficits of ~4 points and other neurobehavioral defects with tooth dentine lead values that exceed 20 to 30 ppm (EPA 1986a). Corresponding average blood lead values would probably be in the range of 30 to 50 μg/dL (EPA 1986a). The study has been reanalyzed in additional reports (Needleman et al. 1982, 1985; Bellinger and Needleman 1983) and critically evaluated by the EPA. In comparison with children having low dentine lead levels (<10 ppm), children having high dentine lead levels (>20 ppm) had significantly lower Full-Scale WISC-R scores (Wechsler Intelligence Scale of Children--Revised), with IQ deficits of ~4 points, and significantly poorer performance on tests of auditory and verbal processing, on a test of attentional performance as measured by reaction time under conditions of varying delay, and on a teachers' behavioral rating (Needleman et al. 1979). The distribution of verbal IQ scores was shifted downward in the

high-lead group, such that none of the children in the high-lead group had verbal IQs >125, whereas 5% of the children in the low-lead group had verbal IQs >125. Furthermore, children in the high-lead group were three times more likely to have a verbal IQ <80 than were children in the low-lead group (Needleman et al. 1982). Using regression analysis, Bellinger and Needleman (1983) found that IQs of children in the high-lead group fell below those expected based on their mothers' IQs and that the amount by which a child's IQ fell below the expected IQ increased with increasing dentine lead levels in what appeared to be a nonlinear manner. That is, dentine lead level was not significantly correlated with IQ residuals in the low-lead children or in the high-lead children with 20 to 29.9 ppm dentine lead, but was significantly correlated with IQ residuals in high-lead children with 30 to 39.9 ppm dentine lead.

Schroeder et al. (1985) and Schroeder and Hawk (1987) evaluated 104 children of lower SES (socioeconomic status) on the Bayley Mental Development Index (MDI) or Stanford-Binet IQ Scale at ages 10 months to 6.5 years. Hierarchical backward stepwise regression analyses indicated that blood lead levels were a significant source of the variance in IQ and MDI scores after controlling for SES and other factors. Fifty of the children were examined again 5 years later, at which time blood lead levels were ≤30 μg/dL. The 5-year follow-up IQ scores were inversely correlated with contemporary and initial blood lead levels, but the effect of lead was not significant after covariates, especially SES, were included in the analysis.

Hawk et al. (1986) and Schroeder and Hawk (1987) replicated this study with 75 black children, 3 to 7 years old, of uniformly low SES. Backward stepwise multivariate regression analysis revealed a highly significant linear relationship between Stanford-Binet IQ scores and contemporary blood lead levels over the entire range of 6 to 47 μg/dL. The association was nearly as striking when past maximum or mean blood lead levels were used. Because SES was uniformly low, it was not a significant covariate. This feature of the study may limit the applicability of the findings to the general U.S. population of children, if SES and lead exposure interact in such a way that IQ is affected by blood lead at lower SES levels but not at high SES levels.

Fulton et al. (1987) studied 501 children, 6 to 9 years old, and of higher and less uniform SES, in Edinburgh, Scotland. A major source of lead exposure in Edinburgh is drinking water. The children were selected from a larger sample of 855 (mean blood lead level: 10.4 μg/dL) by taking all subjects in the top quartile of the blood lead distribution from each of the 18 participating schools plus a random ~1 in 3 subsample of the remaining children. Mean blood lead level of the study population was 11.5 μg/dL, with a range of 3.3 to 34 μg/dL. Blood lead levels >25 μg/dL were found in ten children. Multiple regression analyses revealed a significant inverse correlation between log blood lead and the British Ability Scales Combined score (BACS) and attainment test scores for number skills and word reading after adjustment for confounding variables. Further analysis divided the children into ten groups of ~50 based on blood lead level and plotted the group mean lead values against the group mean difference from the school mean score, adjusted for covariates. The authors reported that this analysis

revealed a dose-effect relationship extending from the mean blood lead level of the highest lead groups, 22.1 μg/dL, down through the mean blood lead level of the lowest-lead group, 5.6 μg/dL, without an obvious threshold.

Other general population studies of reasonably adequate or good quality (Smith et al. 1983; Harvey et al. 1983, 1984; Lansdown et al. 1986; Pocock et al. 1987) have reported no statistically significant effects of lead exposure on IQ or other neurobehavioral measures.

Several prospective studies which focused on neurobehavioral effects of prenatal exposure to lead are summarized in Sect. 4.3.3.2 on developmental toxicity (oral, human).

Robinson et al. (1985) reported evidence of a lead-related decrease in hearing acuity in children. Hearing thresholds at 2,000 Hz increased linearly with maximum historical blood lead levels (6.2 to 56.0 μg/dL) in 75 black children, 3 to 7 years old. The children were healthy and did not have middle ear infections at the time of testing.

Schwartz and Otto (1987) analyzed audiometric results, developmental milestone data (age at which a child first sat up, walked, and spoke, according to parent's recollection) and presence of hyperactivity and speech difficulties in 4,519 children, 4-19 years old, from the NHANES II data set. The analyses included possible covariates or confounding variables that were then available from NHANES(II) data [e.g., race, sex, head-of-household education level, income, dietary factors, indices of iron deficiency and anemia (for developmental milestones), and history of signs of ear infection (for audiometric results)]. Because children's blood lead levels decrease with age but tend to remain in the same percentile within age group, data were analyzed in two different ways: one with current blood lead as independent variable and the other with blood lead percentile rank within age group as independent variable. The possibility of an association between age and audiometric results (hearing threshold) was not addressed. Logistic regression analysis revealed that the probability of elevated hearing thresholds for both ears at 500, 1,000, 2,000, and 4,000 Hz increased significantly with increasing blood lead levels; this relationship was apparent across the entire range of blood lead levels from <4 μg/dL to >50 μg/dL. When the regression analysis used blood lead percentile rank within age group as the independent variable, the association with hearing was not significant. According to the investigators, the lack of association with lead rank indicated that the effect of lead was due to current rather than past lead exposure. The probability that a child was hyperactive increased significantly with increasing blood lead levels (as blood lead percentile rank within age group). The probability of speech impairment, however, was not related to blood lead levels. Linear regression analysis demonstrated that blood lead levels (as blood lead percentile rank within age group) were significantly associated with delays in all three developmental milestones.

Electrophysiological studies have provided evidence suggestive of effects on CNS function at blood lead levels considerably <30 μg/dL, but findings were inconsistent. Linear dose-effect relationships were observed in slow-wave voltage during conditioning in a series of studies

(Otto et al. 1981, 1982, 1985) on the same subjects studied by Schroeder et al. (1985). The association was linear throughout the range of blood lead values (6 to 59 μg/dL). No such relationships were observed in a replicate test (Otto 1986), performed on the same subjects studied by Schroeder and Hawk (1986). Brainstem auditory evoked potential (BAEP) latency (Otto et al. 1985, Robinson et al. 1987), and pattern-reversal visual evoked potential (PREP) latency (Otto et al. 1985, Winneke et al. 1984) and amplitude (Otto 1986, Otto et al. 1985) were also correlated with blood lead levels. The specific components affected and the direction of effect varied across studies.

Effects of lead on peripheral nerve function have been documented in children. Frank peripheral neuropathy has been observed in children at blood lead levels of 60 to 80 μg/dL (Erenberg et al. 1974). Of a total of 14 cases of childhood lead neuropathy reviewed by Erenberg et al. (1974), 5 also had sickle cell disease, a finding which the authors suggested might indicate an increased susceptibility to lead neuropathy among children with sickle cell disease. A case study (Seto and Freeman 1964) reported signs of peripheral neuropathy in a child with a blood lead level of 30 μg/dL, but lead lines in the long bones suggested past exposures leading to peak blood lead levels of ≥40 to 60 μg/dL and probably in excess of 60 μg/dL (EPA 1986a). NCV studies have indicated an inverse correlation between peroneal NCV and blood lead levels over a range of 13 to 97 μg/dL in children living near a smelter in Kellogg, Idaho (Landrigan et al. 1976). The Kellogg, Idaho, data were reanalyzed to determine whether a threshold exists for this effect. Three different methods of analysis (segmental, logistic, and quadratic regressions) revealed evidence of a threshold for NCV at blood lead levels of 20 to 30 μg/dL (Schwartz et al. 1988). A positive association between radial and median NCVs and current (but not umbilical cord) blood lead levels was observed in children with blood lead levels <25 to 30 μg/dL (Winneke et al. 1984).

Oral, animal. The literature on the neurobehavioral effects of oral exposure to lead in animals is extensive, and it has been reviewed in detail and carefully evaluated by the EPA (1986a). Only the studies deemed most pertinent by the EPA (1986a) for clarifying human health issues will be presented here. High levels of exposure to lead produce encephalopathy in several species, but blood lead data for this effect were not available (EPA 1977, 1986a).

A number of histopathological studies of lead's effects on the nervous system of rats treated during early postnatal life with lead acetate or carbonate in the drinking water or diet through their dams or directly, generally for ≤3 weeks, have shown a variety of adverse effects at blood lead levels ranging from 258 to 400 μg/dL. These effects include reductions or delays in the development of the hippocampus (Campbell et al. 1982, Alfano and Petit 1982, Petit et al. 1983, Alfano et al. 1982) and cerebral cortex (Averill and Needleman 1980, Petit and LeBoutillier 1979), reductions in the number and size of axons in the optic nerve (Tennekoon et al. 1979), and demyelination of peripheral nerves (Windebank et al. 1980).

Recent studies have focused on neurobehavioral effects of exposure of the developing organism to lead. Studies concerned primarily with the

effects of prenatal exposure are presented in Sect. 4.3.3 on developmental toxicity, while studies concerned primarily with postnatal exposure are discussed here.

Investigations of the development of motor function and reflexes in rats have shown effects at blood lead levels ≥59 μg/dL. Kishi et al. (1983) treated male rats with lead acetate at 45, 90, or 180 mg/kg/day Pb by gavage on postnatal days 3 to 21 and found that the air righting reflex was significantly delayed at all doses and eye opening was accelerated at the lowest dose tested, which produced a mean blood lead level of 59 μg/dL. Rotorod performance at postnatal day 53 to 58 was significantly impaired at the highest dose, which produced a mean blood lead level of 186 μg/dL. Overmann (1977) reported an adverse effect of lead on rotorod performance at postnatal days 30 to 70 in rats treated by gavage on days 3 to 21 of age with 30 mg/kg/day lead acetate, which resulted in a mean blood lead level of 174 μg/dL, but no effect in rats treated with 10 mg/kg/day lead acetate, which resulted in a mean blood lead level of 33 μg/dL.

Several studies have reported effects on performance in learning tasks in rats with blood lead levels <30 μg/dL. The lowest external exposure level that was significantly associated with a behavioral effect in rats was reported by Bushnell and Levin (1983), who found that exposure of rats starting at postnatal day 21 (postweaning) to drinking water containing 10 ppm lead for 35 days produced a decrease in spontaneous alternation in a radial arm maze. Although blood lead level was not measured, the mean brain lead level on the day following termination of exposure was 0.05 μg/g. By comparison with other studies in which both blood and brain lead levels were measured, the EPA (1986a) estimated that maximum blood lead levels in this study were probably <20 μg/dL.

Other types of tests have also revealed behavioral changes in rats exposed to low levels of lead. Cory-Slechta et al. (1985) reported significant effects in rats exposed after weaning and throughout the course of the experiment to lead acetate at 14.3 ppm lead in their drinking water, which resulted in blood lead levels of 15 to 20 μg/dL. The lead-exposed rats had a significantly higher response rate and a significantly shorter interval between bar-press responses on a fixed-interval operant schedule of food reinforcement. Similar results were obtained at higher exposure levels in a series of earlier studies (Cory-Slechta and Thompson 1979; Cory-Slechta et al. 1981, 1983), even when the operant schedule or contingency for reinforcement was rather different. According to the EPA (1986a), a tendency in lead-treated rats to respond more rapidly (higher response rate, shorter inter-response times, shorter response latency) or to respond even when inappropriate (as when no reward is provided for responses or when reward is specifically withheld for responding) has been reported in many other studies as well, frequently at blood lead levels <30 μg/dL at the time of testing.

Impairment has also been reported at low blood lead levels in other types of behavior/learning studies in rats. In a test of spatial discrimination, Winneke et al. (1977) exposed rats to lead acetate at 745 ppm lead in the diet indirectly via administration to their dams

through gestation and lactation and then directly until testing (at 100 and 200 days of age). The lead-exposed rats were slower to learn the discrimination than were controls. Their blood lead levels at postnatal day 16 averaged 26.6 μg/dL and the levels at 190 days averaged 28.5 μg/dL. Schlipkoter and Winneke (1980) reported that rats exposed in a similar manner, but to 25 or 75 ppm lead in the food until 7 months of age, had significantly poorer performance on a spatial discrimination learning task. Blood lead levels, tested at ~4 months of age, averaged 17.8 and 28.6 μg/dL in the low and high exposure groups; testing was performed at 7 months.

Studies of the effects of lead on learning in monkeys are also available. Bushnell and Bowman (1979a,b), Levin and Bowman (1983), Laughlin et al. (1983), and Mele et al. (1984) have used discrimination reversal tasks to detect impaired learning in monkeys treated orally with lead acetate. Discrimination reversal tasks require the subject to correctly respond to one of two stimuli to get a reward and then, once the task has been mastered, to make the reverse discrimination (i.e., respond only to the cue formerly unpaired with reward). In these studies, monkeys administered lead acetate orally from birth at levels (0.3 or 0.9 mg/kg/day Pb, low- or high-lead) that produced blood lead levels ≥32 μg/dL for 5 months to 1 year were consistently slower in reversal and other learning tasks (Bushnell and Bowman 1979a, Levin and Bowman 1983, Laughlin et al. 1983) even when exposure was terminated at 1 year and the monkeys were tested again at 33 months (Mele et al. 1984) and 49 to 55 months of age (Bushnell and Bowman 1979b). No effects were seen on body weight, growth rate, hematocrit, or general health. The monkeys tested at 49 to 55 months of age had blood lead levels of 4 μg/dL for controls, 5 μg/dL for the low-lead group, and 6 μg/dL for the high-lead group, as compared with average and peak blood lead levels during the year of treatment of 4 and 12 μg/dL for controls, 32 and 70 μg/dL for the low-lead group, and 65 and 134 μg/dL for the high-lead group (Bushnell and Bowman 1979a).

The above findings were supported and extended by other investigators (Rice 1984, 1985a,c; Rice and Willes 1979; Rice and Gilbert 1985; Gilbert and Rice 1987; Rice et al. 1979). These studies demonstrated impaired learning ability on operant conditioning tasks and discrimination reversal tasks and extended the dose-response observations to lower blood lead levels. Monkeys were given a soluble lead compound orally, 5 days/week, from birth throughout the duration of the studies; doses ranged from 0.05 to 2.0 mg/kg/day Pb. Deficiencies in discrimination reversal and/or operant learning were noted in the first 9 months and at 3 to 4 years with the highest dosage (Rice 1985c) and at 421 days through 3.5 years at 0.5 mg/kg/day Pb (Rice and Willes 1979, Rice et al. 1979, Rice 1984). Peak and steady-state blood lead levels were 115 and 33 μg/dL for the 2.0-mg/kg group and 55.3 and 32.8 μg/dL for the 0.5 mg/kg group. Even at the lowest dosages, 0.05 and 0.1 mg/kg/day Pb, the monkeys performed significantly less well in learning discrimination reversals at 3 to 4 years of age, in learning a delayed alternation task at 6 to 7 years of age, and in learning discrimination reversals in the presence of irrelevant cues at 9 to 10 years of age (Rice 1985a,b; Gilbert and Rice 1987). In this series of studies on the same monkeys, peak and steady-state blood lead levels were 15.4 and

10.9 μg/dL for the 0.05 mg/kg group and 25.4 and 13.1 μg/dL for the 0.1 mg/kg group (Rice 1985a, Gilbert and Rice 1987).

In addition to the confirmation (Rice and Willes 1979, Rice 1985a) of Bushnell and Bowman's (1979a,b) observation that lead-treated monkeys were impaired in their ability to learn discrimination reversal tasks, notable findings were the tendency of lead-treated monkeys to respond excessively or inappropriately (e.g., with more responses than controls during times-out) in operant schedules when responses were not rewarded (Rice and Willes 1979). In addition, lead-treated monkeys were also slower to learn reinforcement schedules which required a low rate of responding (Rice and Gilbert 1985), tended to have higher response rates and shorter inter-response times on fixed-interval operant schedules (Rice 1985c), and made more perseverative errors on operant matching-to-sample tasks which required them to direct their responses according to stimulus colors (Rice 1984). These characteristic findings are similar to those in rats, discussed previously.

Electrophysiological studies have reported effects at higher blood lead levels than have the neurobehavioral studies presented above. Suckling rats whose dams were given 0.2% lead acetate (2,000 ppm) in their drinking water had significant alterations in the visual evoked responses (VERs) and decreased scotopic visual acuity at postnatal day 21, at which time their blood lead levels averaged 65 μg/kg (Cooper et al. 1980, Fox et al. 1977, Impelman et al. 1982, Fox and Wright 1982, Winneke 1980). Effects on the nervous system were persistent; decreases in visual acuity and spatial resolution were observed at 90 days of age in rats exposed only from birth to weaning as noted above (Fox et al. 1982).

Dermal. Pertinent data regarding the potential neurobehavioral toxicity of dermal exposure to lead were not located in the available literature.

General discussion. The data on neurobehavioral toxicity of exposure to lead suggest that children are more sensitive, as indicated by responses at lower blood lead levels, than are adult humans, and that animals are affected at roughly the same blood lead levels as are humans.

In humans, encephalopathy can occur at blood lead levels as low as 100 to 120 μg/dL in some adults (Kehoe 1961a,b,c; Smith et al. 1938) and at blood lead levels as low as 80 to 100 μg/dL in some children (NAS 1972, EPA 1986a). This condition can result in death or in permanent cognitive impairment, particularly in children. Furthermore, children with high blood lead levels (>80 to 100 μg/dL) and symptoms of lead poisoning, but no symptoms of acute encephalopathy, also have an increased incidence of lasting neurological and behavioral impairment (EPA 1986a).

Adults have been found to have overt neurological signs and symptoms and impairment on neurobehavioral tests at blood lead levels as low as 40 to 60 μg/dL (Haenninen et al. 1979; Baker et al. 1979, 1983; Zimmermann-Tansella et al. 1983; Campara et al. 1984). These blood lead levels are comparable to those at which other symptoms of lead poisoning, such as gastrointestinal symptoms, occur. Decreased NCVs have

been observed in adults at blood lead levels as low as 30 μg/dL (Seppalainen et al. 1983).

In children with no symptoms of lead intoxication, neurobehavioral impairment, including IQ deficits of ~5 points, has been associated with mean blood lead levels of ~50 to 70 μg/dL (de la Burde and Choate 1972, Rummo 1974, Rummo et al. 1979) and IQ deficits of ~4 points have been associated with blood lead levels of 30 to 50 μg/dL [estimated from dentine lead values and other data by the EPA (1986a)] (Needleman et al. 1979). The highly significant inverse linear relationship between IQ and blood lead levels over the range of 6 to 46 μg/dL found by Hawk et al. (1986) and Schroeder and Hawk (1987) in low-SES black children indicates that IQ decrements may occur without evident threshold down to very low blood lead levels. A study of children of higher and less uniform SES in Edinburgh, Scotland, also reported a significant inverse dose-effect relationship between blood lead level and cognitive ability, with no threshold evident from the mean blood level of 22.1 μg/dL in the highest lead group down to the mean blood lead level of 5.6 μg/dL in the lowest lead group (Fulton et al. 1987). Hence, the lack of threshold in the inverse relationship between blood lead level and cognitive function may pertain not only to low SES children, but also to the general population of children. The data of Fulton et al. (1987) provide evidence of IQ deficits in children with lead exposure at blood lead levels <25 μg/dL (ATSDR 1988). Additional evidence associating neurobehavioral deficits with low blood lead levels of ~10 to 15 μg/dL or possibly lower can be found in studies of the effects of prenatal exposure, discussed in Sect. 4.3.3.2 on developmental toxicity. It should be noted that the effects of blood lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parent's IQ or vocabulary (Fulton et al. 1987, Winneke et al. 1985a) but may have major implications for public health when considered on a population basis (Davis and Svendsgaard 1987, Grant and Davis 1987).

Hearing thresholds in children appear to be affected adversely by lead exposure at low blood lead levels (Robinson et al. 1985, Schwartz and Otto 1987). Robinson et al. (1981) reported that hearing thresholds increased linearly with maximum historical blood lead levels of 6.2-56.0 μg/dL. In the analysis by Schwartz and Otto (1987), the probability of elevated hearing thresholds increased significantly with increasing blood lead level across the entire range of blood lead levels studied (NHANES II data), from <4 μg/dL to >50 μg/dL, with no apparent threshold. Robinson et al. (1985) did not include children with current middle ear infection, but did not mention whether children were examined for chronic middle ear changes, or whether age and other possible confounding variables were controlled in the analysis of hearing threshold data. The analysis by Schwartz and Otto (1987) included history of signs of ear infection as variables, but results of a physical examination for chronic middle ear changes were not available for analysis (Chisolm 1987), and age may have been a confounding variable. Evidence of electrophysiological changes (altered slow-wave voltage during conditioning, changes in evoked potential measures and peripheral nerve conduction velocities) has been observed in children at low blood lead levels (15 to 30 μg/dL and possibly lower) (Otto et al.

1981, 1982, 1985; Otto 1986; Robinson et al. 1987; Winneke et al. 1984; Landrigan et al. 1976).

Studies of animals have shown delays in reflex development in rats during early postnatal life at ≥59 μg/dL (Kishi et al. 1983) and alterations in visual evoked responses and decreased visual acuity in young rats at mean blood lead levels of 65 μg/dL (Cooper et al. 1980, Fox et al. 1977, Impelman et al. 1982, Fox and Wright 1982, Winneke 1980). Decreases in visual acuity persisted through 90 days of age even though exposure was terminated at 21 days of age.

Neurobehavioral effects, measured in various discrimination reversal and operant learning tests, were observed in rats. Blood lead levels as low as 15 to 20 μg/dL were associated with slower learning and higher rates of inappropriate responses (Cory-Slechta et al. 1985, Schlipkoter and Winneke 1980). Similar experiments in monkeys support the findings in rats and extend the dose-response relationship to even lower blood lead levels, comparable to those at which subtle effects are seen in human children. Monkeys given a soluble lead compound at 0.05 mg/kg/day Pb orally from birth until neurobehavioral testing at 3 to 4, 6 to 7, and 9 to 10 years of age had peak and steady-state blood lead levels of 15.4 and 10.9 μg/dL and performed significantly less well in learning discrimination reversal and delayed alternation tasks than did controls (Rice 1985a,b; Gilbert and Rice 1987). In addition, treatment of monkeys orally with lead for the first year of life so as to produce an average blood lead level of 32 μg/dL during that year resulted in neurobehavioral effects that persisted from termination of exposure at 1 year though 49 to 55 months of age, at which time blood lead levels had decreased to 5 μg/dL, virtually the same as control values (Bushnell and Bowman 1979a,b).

4.3.2.3 Cardiovascular toxicity

As in previous sections, occupational exposure will be discussed under inhalation and general population exposure will be discussed under oral, recognizing that these are the major routes of exposure for these categories, but that exposure occurs through the other routes as well.

Inhalation, human. Kosmider and Petelenz (1962) reported that 66% of a group of adults ≥46 years old with chronic lead poisoning of occupational origin had electrocardiographic abnormalities, a rate four times the adjusted normal rate for that age group.

A study of 95 lead smelter workers (mean blood lead levels: 51 μg/dL) and matched unexposed controls (mean blood lead levels: 11 μg/dL) revealed a significantly higher incidence of ischemic electrocardiographic (ECG) changes in the lead workers (20%) than in controls (6%) (Kirkby and Gyntelberg 1985). In addition, a slight (4 to 5 mm Hg) but significant increase in diastolic blood pressure was seen in the lead workers relative to controls. Systolic blood pressure was not affected.

Another occupational study compared 53 lead-exposed male workers (mean blood lead: 47.4 μg/dL, ranging up to 60 to 70 μg/dL) from a plant processing lead and cadmium compounds with a control group of 52 workers (mean blood lead: 8.1 μg/dL, with none exceeding 20 μg/dL) from a

nonlead industry (de Kort et al. 1987). Blood pressure levels were positively correlated with blood lead and urine cadmium levels, but not with blood cadmium levels. The correlation for systolic pressure and blood lead level remained significant after controlling for confounding variables.

A prospective study of 89 Boston policemen revealed that high blood lead level (≥30 μg/dL) was a significant predictor of subsequent elevation in systolic blood pressure (Weiss et al. 1986). Low blood lead level (20 to 29 μg/dL) was not. Diastolic pressure was unrelated to blood lead.

Limited data on occupationally exposed men indicate that the effect of lead on blood pressure may be mediated in part through the renin-angiotensin system, as evidenced through lead-related increases in plasma renin and angiotensin I levels (Campbell et al. 1985) and the kallikrein-kinin system, as indicated by a correlation between renin and kallikrein (Boscolo et al. 1981). The paucity of data associating lead with changes in hormonal systems that regulate blood pressure has stimulated research in animal systems on the mechanism of lead's hypertensive action (discussed in the Oral, animal subsection).

Inhalation, animal. Pertinent data regarding cardiovascular effects of inhalation exposure of animals to lead were not located in the available literature.

Oral, human. Qualitative evidence linking lead exposure to cardiac effects includes the finding of degenerative changes in cardiac muscle, reported as the proximate cause of death in five fatal cases of lead poisoning in young children (Kline 1960). Additional evidence is that electrocardiographic abnormalities are fairly common in cases of childhood lead encephalopathy, but disappear following chelation therapy (EPA 1986a). Silver and Rodriguez-Torres (1968), for example, reported abnormal electrocardiograms in 21 of 30 overtly lead-intoxicated children prior to chelation therapy, but in only 4 of these children after such therapy.

In adults, a study of 75 autopsies of persons who had resided in a soft-water, leached soil region of North Carolina found a positive correlation between lead level in the aorta and death from heart-related disease (Voors et al. 1982). The association persisted after adjustment for the effect of age. A similar correlation was found between cadmium levels in the liver and death from heart-related disease. (Aortic lead and liver cadmium levels were considered to be suitable indices of exposure.) The effects of the two metals appeared to be additive. Potential confounding variables other than age were not included in the analysis. The investigators stated that fatty liver (indicative of moonshine alcohol consumption) and cigarette smoking did not account for the correlations between lead, cadmium, and heart-disease death.

In a case-control study of clinically defined groups, 38 male cardiovascular patients were compared with 48 matched normotensive patients (Khera et al. 1980a). The cardiovascular patients were found to have higher blood lead levels (mean: 44.9 μg/dL) than the normotensive patients (mean: 29.0 μg/dL).

In a study of 431 male civil service employees of the Paris police department, Moreau et al. (1982) and Orssaud et al. (1985) found significant correlations between blood lead levels and systolic blood pressure. Adjusting for covariates, the blood pressure increased consecutively from the first or lowest blood lead group (<12.4 μg/dL) to the fourth (24.8 to 30.8 μg/dL). The overall increase across this range of blood lead levels was 9 mm Hg.

Two large-scale general population studies, the British Regional Heart Study (Pocock et al. 1984, 1985) and the U.S. NHANES II Study (as analyzed by Harlan et al. 1985; Pirkle et al. 1985; Landis and Flegal 1987; Schwartz 1985a,b, 1986a,b), provide convincing evidence of small but statistically significant direct associations between blood lead levels and blood pressure in men (EPA 1986a). Pocock et al. (1984) evaluated relationships between blood lead levels and hypertension in a clinical survey of 7,735 men, age 40 to 49, from 24 British towns. A small but significant correlation between systolic blood pressure and blood lead level was found. Of the 74 men with blood lead levels higher than 37 μg/dL, a higher proportion had systolic or diastolic hypertension than did all other men combined. Reanalysis of the same data resulted in highly significant associations between both systolic and diastolic blood pressure and blood lead levels when adjustments were made for variation due to site (town) in multiple regression analyses (Pocock et al. 1985).

Simple correlational analysis of the NHANES II data by Harlan et al. (1985) revealed statistically significant linear associations between blood lead levels and systolic and diastolic blood pressure for both men and women, age 12 to 74 years. Multiple regression analyses controlling for a number of other potentially confounding factors, however, indicated significant associations between blood lead and blood pressure only for the men.

Additional analyses of the same data set by Pirkle et al. (1985) focused on white males (40 to 59 years of age) in order to avoid the effects of collinearity between blood lead levels and blood pressure evident at younger ages and because of a less extensive database for nonwhites. Multiple regression analyses again revealed significant correlations between blood lead and blood pressure. No threshold was found below which blood lead level was not significantly related to systolic or diastolic blood pressure. Moreover, the analysis by Pirkle et al. (1985) showed that large initial increments in blood pressure occurred at relatively low blood lead levels, with a diminution of blood pressure increments at higher blood lead levels. Lead was a significant predictor of diastolic blood pressure ≥90 mm Hg, the criterion now employed in the United States to define hypertension (EPA 1986a).

Other analyses of the NHANES II data for men have addressed the issue of possible time-trend effects confounded by variations in sampling sites (Landis and Flegal 1987; Schwartz 1985a,b, 1986a,b). These analyses confirm that correlations between systolic or diastolic blood pressure and blood lead levels in men remain significant when site is included as a variable in multiple regression analyses.

Oral, animal. Male rats given 1% (10,000 ppm) lead acetate in their drinking water from 6 to 12 weeks of age had changes in the myocardium, including myofibrillar fragmentation and separation with edema fluid, dilation of the sarcoplasmic reticulum, and mitochondrial swelling (Asokan 1974). Blood lead levels in these rats averaged 112 μg/dL, vs 5 μg/dL in controls.

Male rats given lead acetate at 50 ppm lead in the drinking water for 160 days had markedly increased blood pressure of 182/138 (systolic/diastolic) as compared with 128/98 in controls (Iannaccone et al. 1981). The mean blood lead level of the treated group was 38.4 μg/dL. Male rats administered lead acetate at 5 or 25 ppm lead in the drinking water for 5 months (blood lead levels of 5.6 and 18.2 μg/dL, respectively) did not develop hypertension, although plasma renin activity was increased at 25 ppm (Victery et al. 1982). Other studies reviewed by EPA (1986a) also document increased blood pressure in animals treated orally with lead but apparently did not report blood lead levels. One of these studies, by Perry and Erlinger (1978), reported an increase in systolic blood pressure in rats at a very low exposure level (1 ppm lead in the drinking water for 6 months), but the dietary and drinking water content of essential and nonessential metals was abnormally low and the low-contamination quarters in which the rats were housed also limited their exposure to essential and nonessential metals. These conditions, which result in greater absorption of lead and effects at lower lead intakes than when the diet is less restricted and the living quarters less isolated, may not be as relevant to human exposure.

In reviewing the voluminous database on the mechanism of lead's hypertensive action in animals, EPA (1986a) concluded that although lead, even at very low levels, produces effects on the renin-angiotensin system in animals, these changes are not established as the cause of hypertension. Rather, hypertension is more likely to be due to changes in vascular reactivity and level of sympathetic tone, both of which may be dependent on lead-related changes in intracellular calcium ion concentration (EPA 1986a).

Dermal. Pertinent data regarding cardiovascular effects in humans or animals from dermal exposure to lead were not located in the available literature.

General discussion. The evidence from occupational, clinical, and general population studies suggests that lead affects the cardiovascular system in humans, producing cardiac lesions and electrocardiographic abnormalities at high levels of exposure and increases in blood pressure, particularly in middle-aged men, at very low levels of exposure with no evident threshold through the lowest blood lead levels, 7 μg/dL. The contribution of lead, compared with many other factors which affect blood pressure, appears to be relatively small, usually not accounting for more than 1 to 2% of the variation explained by the models employed when other significant factors are controlled for in the analyses (EPA 1986a).

The animal data support the human data and clearly demonstrate that lead increases blood pressure under controlled experimental conditions.

Interpretation of the blood lead/blood pressure data in epidemiological studies of the general population remains an area of controversy, as reflected in the 1987 Symposium on Lead-Blood Pressure Relationships (*Environmental Health Perspectives*, Vol 78, June 1988) sponsored by the University of North Carolina at Chapel Hill, the International Lead Zinc Research Organization, Inc., EPA, and the American Heart Association. As summarized by Victery et al. (1988), both SJ Pocock and J Schwartz, in considering the evidence from general population epidemiological studies, concluded that a doubling of blood lead level appeared to be associated with an increase of ~1-2 mm Hg in systolic blood pressure. Pocock concluded that the overall evidence from the human studies did not permit the inference of a causal relationship between blood lead and blood pressure. Schwartz concluded that although a causal inference could not readily be drawn from the epidemiological data alone, such an inference was consistent with the animal data. Based on the data for both humans and animals, Schwartz concluded that a causal relationship is likely.

4.3.2.4 Renal toxicity

The characteristics of early or acute nephropathy include nuclear inclusion bodies, mitochondrial changes, and cytomegaly of the proximal tubular epithelial cells; dysfunction of the proximal tubules (Fanconi's syndrome) manifested as aminoaciduria, glucosuria, and phosphaturia with hypophosphatemia; and increased sodium and decreased uric acid excretion. These effects appear to be reversible. Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of tubules and atrophy or hyperplasia of the tubular epithelial cells, and few or no nuclear inclusion bodies, reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The acute form is reported in lead-intoxicated children, whose primary exposure is via the oral route, and sometimes in lead workers. The chronic form is reported mainly in lead workers, whose primary exposure is via inhalation. Animal studies provide evidence of nephropathy similar to that in humans, and particularly to the acute form (Goyer 1985; EPA 1977, 1986a).

Inhalation, human. Richet et al. (1966) reported renal abnormalities in 23 symptomatic lead workers whose blood lead levels ranged from 30 to 87 μg/dL. Biopsies from 21 of these workers showed minor glomerular hyalinization in five workers and major glomerular disease in two workers. Interstitial fibrosis and arteriolar sclerosis were seen in 19 workers and nuclear inclusion bodies in 13 workers. Ballooning of the mitochondria was observed in the proximal tubule epithelial cells.

In a study of 102 cases of occupational lead poisoning, seven cases of clinically verified chronic nephropathy were found (Lilis et al. 1968). Endogenous creatine clearance was <80 μg/dL. The mean blood lead level for the entire study population was 80 μg/dL (range: 42 to 141 μg/dL). Nephropathy was more common among those exposed to lead for more than 10 years than among those exposed for less than 10 years.

Cramer et al. (1974) studied five lead workers exposed for 0.5 to 20 years, whose blood lead levels ranged from 71 to 138 μg/dL. The two

subjects with normal glomerular filtration rates had intranuclear inclusions in the proximal tubules, while the remaining three subjects had decreased glomerular filtration rates, and peritubular fibrosis. Glomeruli were normal in all subjects.

In a study of lead workers, Wedeen et al. (1975, 1979) identified 15 who had no other risk factors for renal disease and who had previously unsuspected lead nephropathy (detected as reduced glomerular filtration rates). Only three of the 15 men had ever experienced symptoms of lead poisoning. Blood lead levels were as follows: >80 μg/dL in one subject, 40 to 80 μg/dL in 11 subjects, and <40 μg/dL in three subjects. Examination of renal biopsies from 12 of these men revealed focal interstitial nephritis in 6, and nonspecific changes, including deformed mitochondria, in the proximal tubules.

The EPA (1986a) concluded that these studies provide evidence for chronic nephropathy being associated with blood lead levels ranging from 40 to >100 μg/dL. It should be noted, however, that blood lead levels measured at the time of renal function testing may not fully reflect the exposure history that contributed to the development of chronic nephropathy in lead workers. Past exposure levels may have been higher.

Inhalation, animal. Pertinent data regarding the renal toxicity of inhalation exposure to lead on animals were not located in the available literature.

Oral, human. Chisolm et al. (1955) and Chisolm (1968) reported that the full Fanconi syndrome was present in some children with lead encephalopathy. According to NAS (1972), the Fanconi syndrome is estimated to occur in ~1/3 of children with encephalopathy and blood lead levels >150 μg/dL. Aminoaciduria occurs at blood lead levels >80 μg/dL in children with acute symptomatic lead poisoning (Chisolm 1962). The aminoaciduria and symptoms of lead toxicity disappeared after treatment with chelating agents (Chisolm 1962).

In a study of children with slight neurological signs indicative of lead toxicity, aminoaciduria was found in eight of 43 children with blood lead levels of 40 to 120 μg/dL (Pueschel et al. 1972). Although blood lead levels were not reported specifically for the children with aminoaciduria, the EPA (1986a) concluded that they were probably at the high end of the range.

A study of adolescents who had been treated for lead intoxication in early childhood (11 to 16 years earlier) revealed no evidence of chronic nephropathy (Chisolm et al. 1976). Blood lead levels during the acute poisoning episode ranged from 100 to 650 μg/dL; all patients received immediate chelation therapy.

The EPA (1986a) concluded, on the basis of these studies, that nephropathy occurs in children only at blood lead levels >80 μg/dL, and usually exceeding 120 μg/dL.

Oral, animal. The EPA (1986a) reviewed a number of studies of renal toxicity of lead in several species, including rats, dogs, monkeys, and rabbits. The results indicate that histopathological changes in the kidneys of lead-treated animals are similar to those in humans, except that glomerular lesions were not reported in the animal

studies. Reduced glomerular filtration rates and aminoaciduria were reported in some of the animal studies.

Dose (blood lead)-effect data are available in the study of Fowler et al. (1980). Rats exposed to lead acetate in the drinking water through the dams during gestation and lactation and then directly until 9 months of age had the following external exposures (ppm Pb), internal exposures (μg/dL Pb in blood), and renal effects: controls--0 ppm, 5 μg/dL, no lesions; 0.5 ppm, 4.5 μg/dL, no lesions; 5 ppm, 11 μg/dL, cytomegaly; 50 ppm, 26 μg/dL, cytomegaly, intranuclear inclusion bodies, and swollen mitochondria; 250 ppm, 67 μg/dL, cytomegaly, intranuclear inclusion bodies, swollen mitochondria, and hemosiderin. These effects occurred in the proximal tubule cells; no lesions were seen in the glomeruli. No evidence of interstitial reaction or of tumor formation was seen.

Dermal. Pertinent data regarding renal toxicity in humans or animals following dermal exposure to lead were not located in the available literature.

General discussion. As discussed in the previous section, the hypertensive effects of lead may be mediated through effects on the kidney. Lead appears to affect vitamin D metabolism in renal tubule cells, such that circulating levels of the vitamin D hormone, 1,25-dihydroxyvitamin D, are reduced. This effect is discussed in a separate section.

4.3.2.5 Interference with vitamin D metabolism

Inhalation. Pertinent data regarding the effects of inhalation exposure to lead on vitamin D metabolism in humans or animals were not located in the available literature.

Oral, human. Lead appears to interfere with the conversion of Vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. This conversion takes place via hydroxylation to 25-hydroxyvitamin D in the liver followed by 1-hydroxylation in the mitochondria of the renal tubule by a complex cytochrome P-450 system (Mahaffey et al. 1982, Rosen and Chesney 1983). Evidence for this effect comes primarily from studies with children, who are exposed to lead mainly by the oral route, although inhalation also contributes to exposure.

Rosen et al. (1980) observed that lead-exposed children with blood lead levels of 33 to 120 μg/dL had marked reductions in serum levels of 1,25-dihydroxyvitamin D. Even in the range of 33 to 55 μg/dL, highly significant depressions in circulating 1,25-dihydroxyvitamin D were found, but the most striking decreases occurred in children whose blood lead levels were ≥62 μg/dL. Children with blood lead levels >62 μg/dL also had significant decreases in serum total calcium and ionized calcium and significant increases in serum parathyroid hormone. Because these conditions would tend to enhance production of 1,25-dihydroxyvitamin D, this finding suggests that production of this hormone was actually impaired (EPA 1986a).

A strong inverse correlation between 1,25-dihydroxyvitamin D levels and blood lead was found over the entire range of blood lead levels measured in the study (12 to 120 μg/dL), with no change in the slope of

the line <30 μg/dL. Serum levels of 1,25-dihydroxyvitamin D returned to normal within 2 days after chelation therapy, while no changes were seen in levels of 25-hydroxyvitamin D (Rosen et al. 1980, 1981; Mahaffey et al. 1982). These results are consistent with an effect of lead on renal production of 1,25-dihydroxyvitamin D.

Oral, animal. Depression of plasma levels of 1,25-dihydroxyvitamin D was observed in rats fed 0.82% lead in the diet as lead acetate for 7-14 days (Smith et al. 1981). High calcium diets protected against this effect. An additional finding was that lead blocked the intestinal calcium transport response to exogenous 1,25-dihydroxyvitamin D, but had no effect on bone response to the vitamin D hormone. Although the lead exposure and resulting blood lead levels (≥174 μg/dL) were high in this study, the results provide support for the observations in children, described above.

Dermal. Pertinent data regarding the effects of dermal exposure to lead on vitamin D metabolism in humans or animals were not located in the available literature.

General discussion. In lead-exposed children with blood lead levels of 33 to 55 μg/dL, 1,25-dihydroxyvitamin D levels were reduced to levels comparable to those observed in children with severe renal insufficiency. In lead-exposed children with blood lead levels of 33 to 120 μg/dL, 1,25-dihydroxyvitamin D levels were depressed to levels (≤20 pg/mL) comparable to those found in vitamin D-dependent rickets, type I--an inborn error of vitamin D metabolism in which the 1-hydroxylase system or component thereof is virtually absent (Rosen et al. 1980, Rosen and Chesney 1983, Chesney et al. 1983). These comparisons are consistent with an effect of lead on the production of 1,25-dihydroxyvitamin D by renal 1-hydroxylase.

The EPA (1986a) has concluded that lead's interference with heme synthesis may underlie the effects on vitamin D metabolism. Evidence that lead affects heme synthesis in the kidney was presented in the section on heme synthesis. In addition, apparent thresholds for the effects of lead on renal vitamin D metabolism and for erythrocyte protoporphyrin accumulation are similar.

Because the vitamin D-endocrine system is responsible in large part for the maintenance of extra- and intracellular calcium homeostasis, it is reasonable to conclude that the interference of lead with renal 1,25-dihydroxyvitamin D production will have an impact on fundamental processes throughout the body (EPA 1986a). The potential impact is presented in Fig. 4.5.

4.3.2.6 Effects on growth

Inhalation. Pertinent data regarding the effects of inhaled lead on postnatal growth in humans or animals were not located in the available literature.

Oral, human. Since the report by Nye (1929) of runting in overtly lead-poisoned children, a number of epidemiological studies have reported an association between blood lead levels and growth in children, who take in lead primarily through the oral route. While these findings were suggestive of an effect, the studies (Mooty et al. 1975,

Johnson and Tenuta 1979, Routh et al. 1979) failed to control for possible confounding factors such as age, race, sex, or nutritional status.

In a study that considered, and ruled out, possible confounding effects of socioeconomic status on lead absorption, Lauwers et al. (1986) compared a set of biometric measurements, including stature and weight, for children with blood lead levels <30 μg/dL and for children with blood lead levels of 40 to 60 μg/dL. When only the children ≤8 years old were considered, the results indicated that slight decreases in biometric values occurred in the high-lead group as compared with the lower-lead group.

Stronger evidence for an association between lead exposure and growth retardation is available in the analyses by Schwartz et al. (1986) of data for 2,695 children ≤7 years old from the NHANES II study. Stepwise multiple regression analyses indicated that blood lead levels (range: 4 to 35 μg/dL) were a statistically significant predictor of childrens' height, weight, and chest circumference, after controlling for age, race, sex, and nutritional covariates. The strongest relationship was observed between blood lead and height, with segmented regression models indicating no evident threshold for the relationship down to the lowest observed blood lead level of 4 μg/dL. Parental stature was not considered as a variable, but analysis showed that age, sex, nutrition, and blood lead level accounted for 91% of the variance in height, and that the addition of blood lead to the most significant model obtained without blood lead accounted for more of the variance and was significant. Schwartz et al. (1986) stated that the mean blood lead level of the children at the average age of 59 months appeared to be associated with a reduction of ~1.5% in the height that would be expected if the blood lead level had been zero. The impact on weight and chest circumference was of the same magnitude.

Lyngbye et al. (1987), in a preliminary report of a cohort study of Danish children of homogenous social/ethnic background joining the first grade in 1982-3, noted that tooth lead was significantly associated with height after controlling for other variables. The investigators concluded that early lead absorption was a risk factor for impaired growth in children. The report did not provide sufficient detail for independent evaluation of the appropriateness of this conclusion.

Oral, animal. The EPA (1986a) concluded from a quick review of 65 relevant animal studies that low-level chronic lead exposure during prenatal or early postnatal life results in retarded growth in the absence of overt signs of lead poisoning.

Dermal. Pertinent data regarding the effects of dermal exposure to lead on growth of humans or animals were not located in the available literature.

General discussion. The EPA (1986a) concluded that the findings of Schwartz et al. (1986) are highly credible. These findings are supported by the results of independent prospective studies of prenatal effects on human development discussed in Sect. 4.3.3 on developmental toxicity and by numerous animal studies. The mechanism of the effect of low-level lead exposure on growth is unknown, but the finding of a suppressed

release of thyrotropin-stimulating hormone (TSH) in response to thyrotropin-releasing hormone (TRH) in two young lead-intoxicated children suggests pituitary involvement (Huseman et al. 1987). In vitro studies with rat pituitary cells showed that lead inhibited the TRH-stimulated release of TSH in a dose-related manner (Huseman et al. 1987), supporting the conclusions drawn from the human data.

4.3.2.7 Effects on the immune system

Inhalation, human. The data are limited to a few studies of immune function in lead workers, whose major exposure is by inhalation, with minor exposure by the oral route. Ewers et al. (1982) reported that lead workers with blood lead levels of 22 to 89 μg/dL (median: 55 μg/dL) have more colds and influenza infections per year and have a significant suppression of secretory IgA levels. Secretory IgA is a major factor in the defense against respiratory and gastrointestinal infections (Koller 1985). Serum immunoglobulin levels were not significantly altered.

Kimber et al. (1986) examined immune function in lead workers exposed occupationally for 4 to 30 years, whose blood lead levels at the time of testing ranged from 25 to 53 μg/dL (mean: 38.4 μg/dL) and controls whose blood lead levels at the time of testing ranged from 8 to 17 μg/dL (mean: 11.8 μg/dL). There were no differences between the workers and controls in serum concentrations of IgG, IgA, or IgM and no correlation between blood lead levels and serum immunoglobulin levels. In addition, response to the mitogen phytohaemagglutinin (an index of T lymphocyte function) and natural killer cell activity were not altered in workers compared with controls.

Inhalation, animal. Phagocytosis of test bacteria by alveolar macrophages was unaffected in lungs of mice exposed to ~13 mg/m^3 of lead chloride by inhalation (Schlipkoter and Frieler 1979). Blood lead data were not available.

Oral, human. The only pertinent data available are for children, whose intake of lead is primarily though the oral route. In a comparison of 12 preschool children having blood lead levels ≥40 μg/dL and elevated free erythrocyte protoporphyrin with seven preschool children without elevated blood lead levels, Reigart and Graber (1976) found no differences between groups with respect to complement levels, immunoglobulin levels, or anti-toxoid titers following booster immunization with tetanus toxoid. Three children with persistently high blood lead levels who were infected with *Shigella enteritis*, however, had prolonged diarrhea (Sachs 1978), indicating the possibility of impaired resistance to infection (EPA 1986a). The small number of children and lack of controls limit the conclusions that can be drawn from this report.

Oral, animal. The EPA (1986a) has reviewed a large number of studies that report effects of orally administered inorganic lead on components of the immune system in animals. Dose-effect data for immune system effects at low levels of external and internal exposure to lead are available from the studies of Luster et al. (1978) and Faith et al. (1979). Prenatal and postnatal exposure of rats to lead acetate at 25 ppm lead in the drinking water (indirectly through their dams and then directly) until testing at 35 to 45 days of age resulted in mean

blood lead levels of 29.3 μg/dL and marked depression of antibody responses to sheep red blood cells, decreased serum IgG (but not IgA or IgM) levels, decreased lymphocyte responsiveness to mitogen stimulation, impaired delayed hypersensitivity reactions, and decreased thymus weights as compared with controls. The 25-ppm exposure was the lowest level tested.

The alkyl lead compound tetraethyl lead reduced antibody titers to sheep red blood cells in mice exposed orally to 0.5 ppm of the compound for 3 weeks (Blakley et al. 1980). Blood lead values were not available.

Dermal. Pertinent data regarding immune system effects of dermal exposure of humans or animals to lead were not located in the available literature.

General discussion. The effects on the immune system of young rats at 29 μg/dL (Luster et al. 1978, Faith et al. 1979) raise the concern that low-level exposure of humans to lead may have adverse effects on the immune system. The best available human data, while not fully adequate to address this issue, gave no indication of immune system effects in children with blood lead levels of ≥40 μg/dL (Reigart and Graber 1976) or in lead workers with blood lead levels of 25 to 53 μg/dL (mean: 38.4 μg/dL) (Kimber et al. 1986).

4.3.2.8 Gastrointestinal toxicity

Inhalation, human. Colic is a consistent early symptom of lead poisoning in occupationally exposed cases (EPA 1986a). Although gastrointestinal symptoms typically occur at the very high blood lead levels associated with encephalopathy, they have sometimes been noted in workers whose blood lead levels were as low as 40 to 60 μg/dL (Haenninen et al. 1979, Baker et al. 1979).

Inhalation, animal. Pertinent data were not located in the available literature.

Oral, human. Colic is a symptom of lead poisoning in children. The EPA (1986a) has identified a lowest-observed-effect level of ~60 to 100 μg/dL for children. This value apparently is based on the NAS (1972) compilation of data from Chisolm (1962, 1965) and Chisolm and Harrison (1956), described in Sect. 4.3.2.2 on neurotoxicity, in which other signs of acute lead poisoning, such as severe constipation, anorexia, and intermittent vomiting, occurred at ≥60 μg/dL.

Oral, animal. Walsh and Ryden (1984) reported that ingestion of lead at levels sufficient to cause renal and hematological toxicity did not appreciably affect gastrointestinal transit time in rats.

Dermal. Pertinent data regarding the effects of dermal exposure to lead on the gastrointestinal tract in humans or animals were not located in the available literature.

General discussion. Although gastrointestinal symptoms have long been considered characteristic of lead poisoning, little attention has been paid to defining dose-effect relationships for this end point, probably because of greater concern for neurotoxic effects. Gastrointestinal symptoms occur in lead workers, whose primary exposure

is by inhalation, and in children, whose primary exposure to lead is oral.

4.3.3 Developmental Toxicity

4.3.3.1 Inhalation

Human. Nordstrom et al. (1979) reported suggestive evidence of a correlation between occupational exposure to lead during pregnancy and decreased birth weights, but did not control for possible confounding variables, including exposure to other toxic substances. Khera et al. (1980b) found positive associations between placental lead concentrations, occupational exposure to lead during pregnancy, and stillbirths; analytical methods in this study may not have been adequate (EPA 1986a). More recent studies of nonoccupationally exposed pregnant women (Sect. 4.3.3.2 on developmental toxicity after oral exposure) provide better data on developmental effects of lead.

Animal. As reviewed by EPA (1986a), Prigge and Greve (1977) exposed rats to a lead aerosol at 1, 3, or 10 mg/m^3 Pb throughout gestation (days 1 to 21). Maternal and fetal ALA-D were inhibited at all exposure levels in a dose-related manner. Fetal, but not maternal, body weight and hematocrit were decreased at 10 mg/m^3, suggesting that the fetuses were more sensitive to lead than were the dams.

4.3.3.2 Oral

Human. Studies by Fahim et al. (1976) and Nordstrom et al. (1978) provided suggestive evidence of an association between nonoccupational prenatal lead exposure and shortened gestation or decreased birth weight, but according to the EPA (1986a), analytical aspects of the Fahim et al. (1976) study were questionable and the study by Nordstrom et al. (1978) failed to control for confounding factors such as socioeconomic status and concurrent exposure to other toxic substances. In addition, other studies of similar quality (Clark 1977, Alexander and Delves 1981, Roels et al. 1978) have found no significant association between prenatal lead exposure and such effects.

In a study of placental element levels in 100 obstetrically normal births (defined as those in which birth weight was within the normal range in regard to gestational age and there were no visible malformations and no important maternal complications), Ward et al. (1987) found statistically significant inverse correlations between placental lead levels and birth weight, head circumference, and placental weight. An inverse correlation with gestational age was not quite significant.

The EPA (1986a) has reviewed in depth several recent human studies that, because of improved analytical techniques for blood lead, large numbers of subjects, and careful consideration of potential confounding factors, provide the best data regarding developmental consequences of low-level prenatal exposure to lead. These consequences include reduced birth weight and gestational age and neurobehavioral deficits or delays. No clear evidence of an association with congenital malformations was found. Prenatal exposure was generally estimated through maternal or cord blood lead concentrations. Exposure of the mothers can be assumed

to have been primarily through the oral route, but with contributions from the inhalation route as well.

The only one of these recent studies to report an association between lead exposure and congenital anomalies is that of Needleman et al. (1984). Using logistic regression modeling techniques and controlling for a number of possible confounders, Needleman et al. (1984) found a statistically significant association between cord blood lead levels and the collective occurrence of minor anomalies in 4,354 infants born in Boston. Data were obtained from hospital records. The most common of these anomalies were hemangiomas and lymphangiomas, minor skin anomalies (tags and papillae), and undescended testicles. No individual anomaly was significantly associated with blood lead levels. Major malformations, birth weight, and gestational age were not associated with blood lead levels. Two other recent studies (McMichael et al. 1986; Ernhart et al. 1985, 1986) reported no association between maternal or cord blood lead levels and congenital malformations.

In a cross-sectional study of 236 mothers and their infants in Glasgow, Scotland, Moore et al. (1982) found reductions in gestational age with increasing cord or maternal blood lead levels. In the 11 cases of premature birth (gestational age <38 weeks), maternal blood lead levels averaged ~21 μg/dL and cord blood lead levels averaged ~17 μg/dL at delivery. The overall geometric mean blood lead levels at delivery were: maternal, 14 μg/dL; cord, 12 μg/dL. Stepwise forward multiple regression analyses showed significant negative coefficients for length of gestation against log-transformed maternal or cord blood levels. Birth weight was not associated with blood lead levels. First-flush household water lead concentrations were positively associated with maternal and cord blood lead levels.

An ongoing prospective study of the effects on child development of prenatal and postnatal lead exposure in the lead smelter town and environs of Port Pirie, South Australia, provides information on congenital anomalies, length of gestation, birth weight, and stillbirth or miscarriage (McMichael et al. 1986) and on neurobehavioral development (Vimpani et al. 1985, 1987; Baghurst et al. 1987). McMichael et al. (1986) studied 831 pregnant women and followed 774 of the pregnancies to completion. Blood lead levels during pregnancy and at delivery were significantly higher in women who lived in Port Pirie than in those who lived in adjacent towns and rural areas (e.g., at delivery: 11.2 μg/dL, Port Pirie vs 7.5 μg/dL, outside). No association between lead exposure and the occurrence of congenital anomalies was found when pertinent risk factors, such as smoking and alcohol consumption were controlled for. Multivariate analysis revealed a significant association between preterm delivery (before the 37th week of pregnancy) and maternal blood lead levels at delivery. The relative risk of preterm delivery increased over fourfold at blood lead levels >14 μg/dL compared with relative risk of 1 at blood lead levels of ≤8 μg/L. The incidence of low birth weight (<2,500 g at gestational age ≥37 weeks) was greater in the Port Pirie group than in the outside group, but maternal and cord blood lead levels at delivery were somewhat lower in the low-birth-weight pregnancies. Similarly, 22 of the 23 miscarriages and 10 of the 11 stillbirths in this study occurred in the Port Pirie mothers, but the

average maternal blood lead level at delivery was significantly lower for stillbirths than for live births.

Preliminary results of blood lead and neurobehavioral testing of 592 children from the Port Pirie study were reported by Vimpani et al. (1985, 1987) and Baghurst et al. (1987). In these children, geometric mean blood lead levels increased from ~14 μg/dL at 6 months of age to ~21 μg/dL at 15 and 24 months. At 24 months, ~20% of the children had blood lead levels >30 μg/dL. Neurobehavioral tests--the Bayley Mental Development Index (MDI) and Bayley Psychomotor Development Index (PDI)--were conducted at 24 months. Multiple regression analyses indicated that reduced MDI scores were significantly associated with higher integrated postnatal blood lead levels and with 6-month blood lead levels, but not with prenatal delivery or cord blood lead levels. Controlling for both maternal IQ and HOME scores, the association between 6-month blood leads and 24-month MDI scores remained significant, with a 2-point deficit in MDI for every 10 μg/dL increase in blood lead. Follow-up of this cohort involved blood lead testing at 3 and 4 years of age and neurobehavioral assessment using the McCarthy Scales of Children's Abilities (McMichael et al. 1988). Multiple regression analyses showed that childrens' scores on the McCarthy General Cognitive Index (GCI) were significantly and inversely correlated with log blood lead levels at 6, 24, and 36 months and with the integrated average for birth to 4 years. The estimated decrease in GCI score was ~7.2 points for an increase in integrated average blood lead from 10-30 μg/dL.

In another prospective study, Bellinger et al. (1984, 1985a,b, 1986a,b, 1987a,b) determined cord blood lead levels at delivery, and measured blood lead levels and MDI and PDI scores every 6 months thereafter on 249 middle- to upper-middle-class Boston children. Infants of <34 weeks gestational age were excluded from the study. Cord blood lead values were <16 μg/dL for 90% of the subjects, with the highest value being 25 μg/dL. On the basis of cord blood lead levels, the children were divided into low (<3 μg/dL; mean: 1.8 μg/dL), medium (6 to 7 μg/dL; mean: 6.5 μg/dL) and high (≥10 μg/dL; mean: 14.6 μg/dL) exposure groups. A slight but not significant direct correlation between cord blood lead category and length of gestation was seen, but analysis within gestational age categories indicated no interaction between cord blood lead category and length of gestation (Bellinger et al. 1984, 1985a). The percentage of small-for-gestational age infants increased with increasing cord blood lead, although the trend was not quite statistically significant (Bellinger et al. 1984). Multivariate regression analysis revealed an inverse correlation between cord blood lead levels and MDI scores at 6, 12, 18, and 24 months of age (Bellinger et al. 1985, 1986a,b, 1987a). The high lead group had an average deficit of 4.8 points on the covariate-adjusted MDI score as compared with the low lead group. MDI did not correlate with postnatal blood lead levels. No correlations between PDI and cord or postnatal blood lead levels were seen. Additional follow-up showed deficits in MDI scores of these children at ~5 years of age, which correlated significantly with earlier blood lead levels (at 24 months of age) rather than with concurrent or prenatal blood lead levels (Bellinger et al. 1987b).

Dietrich et al. (1986, 1987b) reported interim results for 185 subjects and later results from the complete follow-up sample of 305 subjects (Dietrich et al. 1987a) in a prospective study of inner-city children born in Cincinnati, Ohio. Maternal blood lead levels were measured at the first prenatal visit; cord blood was measured at delivery; infant blood lead levels were measured at 10 days and 3 months of age; and neurobehavioral tests were performed at 3 and 6 months of age. Mean blood lead levels were as follows: prenatal (maternal)--8.0 μg/dL (range: 1 to 27 μg/dL); umbilical cord--6.3 (range: 1 to 28); 10-day and 3-month infant--4.6 and 5.9 μg/dL (range: 1 to 22 μg/dL for each). Multiple regression analyses, with perinatal health factors such as birth weight and gestation treated as confounders, showed inverse correlations between prenatal or cord blood lead levels and performance on the MDI at 3 months and between prenatal or 10-day neonatal blood lead levels and performance on the MDI at 6 months. No significant correlation of blood lead level with PDI was seen. Male infants and low SES infants appeared to be more sensitive to the effect on MDI. Multiple regression analyses for male or low SES infants showed covariate-adjusted decrements of 0.84 or 0.73 MDI points per μg/dL of prenatal or 10-day neonatal blood lead, respectively (i.e., ~8 points deficit for a 10-μg/dL increase in blood lead) (Dietrich et al. 1987a).

Further analyses by structural equation modeling showed that the effect of prenatal lead exposure on MDI was in part mediated through its effects on birth weight and gestational age. Higher prenatal blood lead levels were associated with reduced birth weight and reduced gestational age, which were each significantly associated with reduced MDI scores (Dietrich et al. 1987a). Separate, preliminary analyses of the data from the Cincinnati study by Bornschein et al. (1987) indicated that for each natural log unit increase in blood lead, the decrease in birth weight ranged from 58 to 601 g, depending on the age of the mother. The authors reported that the threshold for this effect could be ~12 to 13 μg/dL. In addition, a decrease in birth length of 2.5 cm per natural log unit of maternal blood lead was seen, but only in white infants.

Further follow-up of 260 infants from the Cincinnati cohort revealed that postnatal growth rates, measured as covariate-adjusted increases in stature from 3 to 15 months of age, were inversely correlated with postnatal increases in blood lead levels from 3 to 15 months of age (Shukla et al. 1987). This relationship was significant only for infants with relatively higher prenatal lead exposures (i.e., those whose mothers had prenatal blood lead levels ≥7.7 μg/dL).

In a prospective study of mothers and infants in Cleveland, Ohio (Ernhart et al. 1985, 1986, 1987; Wolf et al. 1985), mean blood lead levels at the time of delivery were 6.5 μg/dL (range: 2.7 to 11.8 μg/dL) for 185 maternal samples and 5.8 μg/dL (range: 2.6 to 14.7 μg/dL) for 162 cord samples. There were 132 mother-infant pairs of data. The infants were evaluated for anomalies using a systematic, detailed protocol and for neurobehavioral effects using the Brazelton Neonatal Behavioral Assessment Scale (NBAS) and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R), including a Neurological Soft Signs scale. Hierarchical regression analysis was performed. No evidence of an association between blood lead levels and morphological anomalies was found. Using the complete set of data, abnormal reflexes and

neurological soft signs were significantly related to cord blood lead levels and muscle tonus was significantly related to maternal blood lead level. Using data from the mother-infant pairs, the only significant association found was between the Neurological Soft Signs score and cord blood lead levels; no association with maternal blood lead levels was seen (Ernhart et al. 1985, 1986). A brief, preliminary report on later outcomes from this study mentioned a significant association between the Neurological Soft Signs measure and the MDI scores at 12 months (Wolf et al. 1985).

A later analysis (Ernhart et al. 1987) related blood lead levels obtained at delivery (maternal and cord blood) and at 6 months, 2 years, and 3 years of age to developmental measures [MDI, PDI, KID (Kent Infant Development Scale), and Stanford-Binet IQ] administered at 6 months, 1 year, 2 years, and 3 years of age as appropriate. After controlling for covariates and confounding risk factors, the only significant associations of blood lead with concurrent or later development were an inverse association between maternal (but not cord) blood lead and MDI, PDI, and KID at 6 months, and a positive association between 6-month blood lead and 6-month KID. The investigators concluded that, taken as a whole, the results of the 21 analyses of correlation between blood lead and developmental measures were "reasonably consistent with what might be expected on the basis of sampling variability," that any association of blood lead level with measures of development was likely to be due to the dependence of both blood lead and development on the caretaking environment, and that if low-level lead exposure has an effect on development, the effect is quite small. Ernhart et al. (1987) also analyzed for reverse causality: i.e., that developmental deficit or psychomotor superiority in infants at 6 months of age contributed to increases in subsequent blood lead levels. No significant correlations were observed when covariates were controlled.

Winneke et al. (1985a,b) investigated the predictive value of different markers of lead exposure for neurobehavioral performance [WISC Verbal, Performance and Full-scale IQs; Wiener (Vienna) reaction performance tests; Cued Reaction Time]. This investigation involved the follow-up, at 6 to 7 years of age, of 114 children out of an original study population of 383 children born in Nordenham, Federal Republic of Germany. At delivery, the mean maternal blood lead level was 9.3 μg/dL (range: 4 to 31 μg/dL) and the mean cord blood lead level was 8.2 μg/dL (range: 4 to 30 μg/dL). Cord and maternal blood lead levels were highly correlated. Stepwise multiple regression analyses indicated that maternal blood lead levels accounted for nearly as much of the variance in neurobehavioral test scores at 6 to 7 years as did contemporary blood lead levels; with either exposure marker, significance was seen only in increased errors on the Wiener Reaction Performance tests.

Bonithon-Kopp et al. (1986) reported that maternal and infant hair lead levels, determined from hair samples taken at birth, correlated inversely with results on neurobehavioral tests (McCarthy Scales of Children's Abilities) when the children were tested at 6 years of age. Other studies have also reported associations between hair lead levels and behavioral or cognitive test scores, but measures of hair lead are questionable in terms of accurately reflecting internal body burdens,

and such data cannot be used to evaluate internal dose-response relationships (EPA 1986a).

A few studies have reported associations between prenatal lead exposure and changes in heme metabolism. In a study of 294 mother-infant pairs, Haas et al. (1972) reported mean blood lead levels of 16.98 μg/dL for mothers and 14.98 μg/dL for newborns. Infant blood lead levels and urinary ALA were positively correlated. Kuhnert et al. (1977), in a study of pregnant urban women, found that cord erythrocyte lead levels ranged from 16 to 67 μg/dL of cells (mean: 32.9 μg/dL) and were inversely correlated with ALA-D activity, as were maternal erythrocyte lead levels. In a study of 500 mothers at delivery, Lauwerys et al. (1978) reported negative correlations between blood lead levels and ALA-D activity in both mothers and their infants (cord blood). No correlation between blood lead level and erythrocyte protoporphyrin was seen. Blood lead levels averaged 10.2 μg/dL with a range of 3.1 to 31 μg/dL in the mothers and 8.4 μg/dL with a range of 2.7 to 27.3 μg/dL in the infants. Taken together, the results of these studies indicate that ALA-D activity may be a more sensitive indicator of lead effects on fetal heme synthesis than are erythrocyte protoporphyrin or urinary ALA levels (EPA 1986a).

Animal. Twenty-three teratogenicity studies in which lead compounds (acetate or nitrate) were administered in the drinking water or feed or by gavage to rats and mice have shown no evidence that lead causes malformations, but some evidence that lead causes fetotoxic effects. These studies are summarized by the EPA (1986a).

The teratogenicity studies most relevant to current concerns for human prenatal exposure will be reviewed below, along with studies that were concerned primarily or exclusively with neurobehavioral effects of prenatal exposure to lead. In rodents, a greater proportion of the development of the nervous system takes place postnatally than is the case in humans. Accordingly, studies of developmental neurobehavioral toxicity in rodents that extend exposure into the early postnatal period are probably more analogous to human prenatal exposure than are rodent studies that use only prenatal exposure.

Miller et al. (1982) administered doses of up to 100 mg lead acetate/kg/day (63.7 mg/kg/day Pb) to rats before breeding and throughout pregnancy. The only effect seen was fetal stunting at the high dose. Maternal blood lead values ranged from 80 to 92 μg/dL prior to mating and from 53 to 92 μg/dL during pregnancy. Pretreatment and control blood lead levels averaged 6 to 10 μg/dL.

Rabe et al. (1985) exposed female rats to 5,000 ppm lead acetate in the drinking water prior to mating and throughout gestation. The pups were transferred to unexposed foster dams on the second day after birth. Mean blood lead levels were 98 μg/dL at day 1 and 20 μg/dL at day 16 of age in pups from treated dams and ~10 μg/dL at both ages in pups from control dams. Body weights were reduced in treated pups relative to controls at birth but not at 30 days of age. Neurobehavioral function (surface righting and negative geotaxis reflexes, spatial discrimination, and reversal in T-maze), tested in the pups at 17 days of age, was not affected by prenatal lead treatment.

Kimmel et al. (1980) and Grant et al. (1980) reported different aspects of a study of prenatal, postnatal, and long-term exposure of rats to lead. This well-conducted study provided a variety of relevant dose-effect information. In this study, female rats were exposed to lead acetate in the drinking water at 0.5, 5, 25, 50, or 250 ppm lead from weaning through mating, gestation, and lactation. The pups were weaned onto the same drinking water solutions as their dams received. In addition, some of the dams were killed at day 21 to 22 of gestation for evaluation of the fetuses and uteri. Toxicity to the dams (dose-related slight depression of body weight and delay in time of vaginal opening) was seen at ≥25 ppm; the effects at 25 ppm were of marginal significance. No significant differences in indices of embryo- or fetotoxicity or teratogenicity were seen in treated groups relative to controls. Length of gestation and birth weights were unaffected, but mean crown-rump length of 1-day-old female pups in the 250-ppm group was significantly shorter than in controls. Median blood lead levels just prior to mating and at day 21 of gestation were 1 and 4 μg/dL for controls, 9 and 12 μg/dL for the 5-ppm group, 20 and 23 μg/dL for the 25-ppm group, 24 and 35 μg/dL for the 50-ppm group, and not reported for the 250-ppm group (Kimmel et al. 1980).

Grant et al. (1980) reported significant delays in vaginal opening in female pups of groups receiving ≥25 ppm lead and significant delays in the development of surface and air righting reflexes in pups of the 50- and 250-ppm lead groups. Blood lead levels of the pups at 1 and 11 days were 4 and 3 μg/dL, controls; 37 and 22 μg/dL, 25-ppm pups; 57 and 35 μg/dL, 50-ppm pups; and not reported, 250-ppm pups. In comparing the results of this study with results of the study by Rabe et al. (1985), in which no effects on the development of reflexes were seen at a much higher level of lead in the drinking water, it should be noted that exposure to lead in the Rabe et al. (1985) study ceased shortly after birth, but in the Grant et al. (1980) study exposure to lead continued through the time of testing.

Reiter et al. (1975) observed delays in development of the righting reflex in rat pups whose dams were exposed to lead acetate at a concentration of 5 or 50 ppm lead in their drinking water throughout gestation and lactation. Eye opening was delayed at the higher exposure level. Blood lead levels were not determined.

Taylor et al. (1982) found that exposure of female rats from before mating though gestation and lactation to 200 or 400 ppm of lead acetate in the drinking water did not result in significant differences in the pups' acquisition of a behavioral response when tested at 11 days of age, but did result in significantly slower extinguishing of the response when the reward was no longer provided. Blood lead levels at 21 days of age were 3.7 μg/dL in controls, 38.2 μg/dL in the low exposure group, and 49.9 μg/dL in the high exposure group.

Bushnell and Bowman (1979c) and Levin and Bowman (1983) reported different aspects of a study in which adult female monkeys were treated orally with 3 or 6 mg/kg/day of lead acetate prior to mating and throughout gestation. Treatment of the mothers produced no changes in early social behavior of their infants and no differences in learning ability, relative to controls, when the offspring were tested on a

search task at 4 to 5 years of age. Blood lead levels at birth were 5, 30, and 55 μg/dL in control (N = 5), low lead (N = 3), and high lead (N = 4) groups, respectively.

Histological changes have been reported in the brains of rat pups at much higher blood lead levels than those reported above. Administration of 2,000 ppm of lead chloride in the drinking water to pregnant rats during gestation and lactation was reported to produce a less mature synaptic profile in the cerebral cortex of the pups at postnatal day 15 (McCauley and Bull 1978, McCauley et al. 1979) and a 30% reduction in synaptic density in the cerebral cortex at postnatal day 15 but not day 21 (McCauley et al. 1982). Blood lead levels were 80 μg/dL at birth.

Murray et al. (1978) observed decreased numbers of dendritic spines and malformed spines in brain parietal cortex at postnatal day 30 in pups whose mothers were administered 255 to 478 mg/kg/day Pb from lead acetate in drinking water during gestation and lactation. Blood lead levels were not reported.

Some studies have investigated the effects of prenatal exposure to lead on heme metabolism. Hubermont et al. (1976) administered lead nitrate at a concentration of 1 or 10 ppm of lead in drinking water to female rats before mating, throughout gestation, and during lactation. Blood lead levels in the dams and pups of the 10-ppm group were 68 and 42 μg/dL, respectively. An increase in free tissue porphyrins and a decrease in ALA-D activity was seen in the pups of the 10 ppm group, as compared with controls.

Hayashi (1983) reported effects at even lower external and internal exposure levels. Lead acetate at 5 ppm lead in the drinking water of rats for the first 18 or 21 days of pregnancy resulted in decreased ALA-D activity in the fetal and maternal erythrocytes and increased ALA-D activity in fetal but not maternal liver. Fetal, but not maternal, hematocrits and hemoglobin levels were decreased in the 21-day treated group. Fetal blood lead levels were 27 μg/dL in the 18-day and 19 μg/dL in the 21-day treated groups. Maternal blood lead levels were ~4 μg/dL in treated and control groups.

Organolead compounds have undergone limited testing for developmental toxicity. McClain and Becker (1972) treated pregnant rats orally with total doses of 7.5 to 30 mg/kg tetraethyl lead, 40 to 160 mg/kg tetramethyl lead, or 15 to 38 mg/kg trimethyl lead chloride, given in three divided doses on gestation days 9 to 11 or 12 to 14. These doses correspond to 1.6 to 3.2 mg/kg/day Pb for tetraethyl lead, 10 to 28.7 mg/kg/day Pb for tetramethyl lead, and 3.7 to 7.2 mg/kg/day Pb for trimethyl lead chloride (EPA 1986a). All three compounds resulted in maternal death at the highest doses and maternal toxicity at the lower doses. Fetal body weights were decreased, relative to controls, at all dose levels. No teratogenic effects were observed. Kennedy et al. (1975) administered tetraethyl lead by gavage to mice and rats on days 6 to 16 of gestation at 0.1, 1.0, or 10 mg/kg/day (0.064, 0.64, or 6.4 mg/kg/day Pb). Maternal toxicity, prenatal mortality, and developmental retardation were observed in both species at the highest dose, which was discontinued after 3 days because of excessive toxicity. Maternal and fetal toxicity also occurred in both species at the middle dose and

results were negative in both species at the lowest dose. Blood lead levels were not reported.

4.3.3.3 Dermal

Pertinent data regarding the developmental toxicity of dermal exposure to lead in humans or animals were not located in the available literature.

4.3.3.4 General discussion

According to the EPA (1986a), evidence from the three recent human studies that included malformations as an end point (Needleman et al. 1984; McMichael et al. 1986; Ernhart et al. 1985, 1986) allows no definitive conclusion regarding the existence of an association between prenatal lead exposure in humans and the occurrence of congenital anomalies. The use of hospital records as the source of data on anomalies in the studies by Needleman et al. (1984) and McMichael et al. (1986) could result in a lack of precision and uniformity. The investigation by Ernhart et al. (1985, 1986), on the other hand, used a detailed protocol for the detection of anomalies, but the restricted range of maternal and cord blood lead levels (2.7 to 11.8 μg/dL and 2.6 to 14.7 μg/dL, respectively) would mean that any effect would be likely to be subtle and the relatively small number of subjects in the study would not be sufficient for the detection of differences in low frequencies of anomalies. Similarly, the number of subjects in the study by McMichael et al. (1986) may not have been adequate to detect infrequent birth defects.

Teratogenicity studies in rats and mice (one inhalation study and 23 oral studies) provide no evidence that lead compounds (acetate or nitrate) are teratogenic when exposure is by natural routes. Intravenous or intraperitoneal injection of lead compounds (acetate, chloride, or nitrate) into pregnant rats, mice, or hamsters has produced malformations in several studies reviewed by EPA (1986a).

The evidence for an adverse effect of prenatal lead exposure on birth weight is limited. Dietrich et al. (1986, 1987a) and Bornschein et al. (1987) reported a significant inverse association between prenatal maternal blood lead levels and birth weight in the Cincinnati study. The reduction in birthweight was apparent at blood lead levels as low as 12 to 13 μg/dL. Bellinger et al. (1984) found that the percentage of small-for-gestational age infants increased with increasing cord blood lead, although the trend was not quite statistically significant. Needleman et al. (1984), Moore et al. (1982), and Ernhart et al. (1985, 1986), observed no association between maternal or cord blood levels and birth weight. McMichael et al. (1986), however, reported significant direct associations between maternal and cord blood lead levels and birth weight.

The results of McMichael et al. (1986) are puzzling because the proportion of Port Pirie pregnancies (delivery maternal blood lead = 10.4 μg/dL) resulting in low-birthweight infants was more than twice that for outside pregnancies (delivery maternal blood lead = 5.5 μg/dL). Yet the maternal and cord blood lead levels were somewhat lower in low-birth-weight pregnancies than in pregnancies with birth weights >2500 g.

A similar phenomena was seen with regard to stillbirths, which occurred primarily in the Port Pirie pregnancies, but which were associated with lower maternal blood lead levels than were live births. Davis and Svendsgaard (1987) suggested that the anomalous findings for blood lead vs birth weight or stillbirth in the Port Pirie study suggest an increased transfer of lead from mother to fetus, which is toxic to the fetus. This suggestion is supported by the inverse correlation between placental lead levels and birth weight, head circumference, and placental weight reported by Ward et al. (1987) and the increased levels of lead in the placenta reported by Wibberly et al. (1977) in cases of stillbirth and neonatal death. Alternatively, Wibberly et al. (1977) has suggested that such findings may indicate that lead accumulates in the placenta in times of fetal stress.

The evidence from the above studies indicates that gestational age may be reduced as prenatal lead exposure increases, even at blood lead levels below 15 μg/dL (EPA 1986a). Moore et al. (1982), McMichael et al. (1986), and Dietrich et al. (1986, 1987a) reported significant negative correlations between maternal or cord blood lead levels and gestational age. Based on parameter estimates of Dietrich et al. (1986), the reduction in gestational age was 0.6 week per natural log unit of blood lead increase (EPA 1986a). Based on risk estimates of McMichael et al. (1986), the risk of preterm delivery increases by at least fourfold as either cord blood or maternal blood lead level at delivery increases from ≤8 to >14 μg/dL. Needleman et al. (1984) and Bellinger et al. (1984), however, did not find a significant relationship between maternal or cord blood lead level and gestational age.

The above human studies, considered together, provide clear evidence of a deleterious effect of prenatal lead exposure on neurobehavioral development. Bellinger et al. (1984, 1985a,b, 1986a,b, 1987a) reported significant deficits of 4.8 points in MDI scores at ages 6 to 24 months in children whose blood lead level at birth was 10 to 25 μg/dL, in comparison with children whose blood lead level at birth was <3 μg/dL. Dietrich et al. (1987a) reported dose-related deficits in MDI scores at 6 months for male infants of 0.84 MDI points for each μg/dL increase in prenatal blood lead and for low SES infants of 0.73 MDI points for each μg/dL increase in 10-day neonatal blood lead (EPA 1986a). Male and low SES infants were more sensitive to prenatal exposure to lead, as indexed by prenatal and neonatal blood lead levels (Dietrich et al. 1986, 1987a).

Vimpani et al. (1985, 1987) and Baghurst et al. (1987), on the other hand, found that deficits in MDI scores were more closely related to postnatal lead exposure than to prenatal exposure. They ascribed an average 2-point drop in MDI scores at 24 months of age to a mean increase of 10 μg/dL in blood lead levels at 6 months of age. According to the EPA (1986a) and Davis and Svendgaard (1987), later increases in exposure, by ~50% from 6 to 15 months of age, may have overwhelmed the more subtle effects of lower prenatal exposure levels. Follow-up of this cohort through 4 years of age indicated that integrated postnatal blood lead levels were inversely correlated with McCarthy GCI scores such that a blood lead level of 30 μg/dL corresponded to a GCI score 7.2 points lower than at a blood lead level of 10 μg/dL (McMichael et al. 1988).

Ernhart et al. (1985, 1986) provided evidence relating neonatal performance on a Neurological Soft Signs scale to cord blood lead levels. A preliminary report of follow-up studies indicated that lowered MDI scores at 1 year of age were associated with the Neurological Soft Signs measure (Wolf et al. 1985). Hence, it is possible to infer an indirect effect of cord blood lead on MDI (EPA 1986a, Davis and Svendsgaard 1987), although Ernhart et al. (1985, 1986) did not reach such a conclusion. The effects noted by these investigators were significantly related to cord blood lead levels that averaged 5.8 μg/dL and ranged upward to only 14.7 μg/dL. Later analysis and follow-up of the children for blood lead and developmental measures through 3 years of age revealed significant inverse associations between maternal (but not cord) blood lead and MDI, PDI, and KID at 6 months (Ernhart et al. 1987).

Winneke et al. (1985a,b) found that errors in the Wiener Reaction Performance test were associated with maternal blood lead levels averaging 9.3 μg/dL and cord blood lead levels averaging 8.2 μg/dL. The EPA (1986a) concluded from a scatter plot of mother-cord blood lead levels that, except for a couple of outliers, nearly all of the values were <20 μg/dL and generally did not seem to exceed ~15 μg/dL.

The EPA (1986a), Davis and Svendsgaard (1987), Grant and Davis (1987), and ATSDR (1988) concluded that the evidence from these studies of neurobehavioral effects of prenatal lead exposure suggests that neurobehavioral deficits are associated with prenatal internal exposure levels, as indicated by maternal or cord blood lead concentrations, of ~10 to 15 μg/dL, and possibly even lower. Although a 2- to 8-point decline in MDI score for an individual child may not be clinically significant, a 4-point downward shift in a normal distribution of MDI scores of a population of children would result in 50% more children scoring below 80, a consequence of great concern to public health (Davis and Svendsgaard 1987, Grant and Davis 1987). Additional evidence of an association between relatively low blood lead levels and neurobehavioral effects in children is reported in Sect. 4.3.2.2 on neurobehavioral toxicity, in which postnatal exposure is discussed.

Some of the studies of neurobehavioral and development effects discussed in this section on developmental toxicity and in the previous section on neurobehavioral toxicity have been criticized for methodological flaws, including handling of cofactors (EPA 1986a, Ernhart 1988). ATSDR (1988) and EPA (1986a) have taken such criticisms into account and have concluded that the findings associating relatively low blood lead levels with neurobehavioral and developmental effects in children are nonetheless cause for concern. In addition, it should be noted that some of the negative studies have also been criticized for methodological flaws that bias towards Type II (false negative) errors (Needleman 1987, Needleman and Bellinger 1987). Although no single study associating low blood lead levels with reduced cognitive performance in children is definitive, a metaanalysis of 13 studies providing data on an inverse relationship between blood lead and children's IQs concluded that the joint probability of obtaining the reported results was less than 3 in a billion (Needleman 1987, Needleman and Bellinger 1987).

Animal studies also provide evidence of neurobehavioral toxicity of prenatal exposure to lead. Blood lead levels associated with neurobehavioral effects in rats were ≥35 μg/dL, somewhat higher than those in the human studies (Grant et al. 1980, Taylor et al. 1982). Monkeys, however, did not show effects from prenatal exposure to lead at blood lead levels of 30 to 55 μg/dL on early social behavior or on learning ability at 4 to 5 years of age (Bushnell and Bowman 1979c, Levin and Bowman 1983).

In contrast to animal studies of prenatal exposure, animal studies of postnatal exposure, presented in Sect. 4.3.2.2 on neurobehavioral toxicity, show effects at blood lead levels similar to those associated with effects in humans.

4.3.4 Reproductive Toxicity

4.3.4.1 Inhalation

Human. As reviewed by the EPA (1986a), severe occupational exposure to lead has long been known to be associated with a high likelihood of spontaneous abortion in pregnant women, and this observation led to the exclusion of women from high-exposure occupations. Early studies of this phenomenon, however, suffer from methodological inadequacies and the lack of dose-effect information. Occupationally exposed populations receive the bulk of their exposure through inhalation, with some exposure through the oral route as well.

Nordstrom et al. (1978) found an increased frequency of spontaneous abortion in women living closest to a lead smelter. In addition, Nordstrom et al. (1979) reported that female workers at the smelter had an increased frequency of spontaneous miscarriage when employed at the smelter during pregnancy or when employed at the smelter prior to pregnancy and still living near the smelter. Women who worked in more highly contaminated areas of the smelter were more likely to have aborted than were other women. These studies were confounded by the presence of other toxic agents and by the lack of matching for socioeconomic status, which could also bear on the women's health (EPA 1986a).

Based on data of Lancranjan et al. (1975) and Wildt et al. (1983), the EPA (1986a) concluded that reproductive effects (on sperm or testes) may occur in men as a result of chronic exposure at blood lead levels of 40 to 50 μg/dL. Lancranjan et al. (1975) studied a group of 150 workmen with long-term lead exposure, categorized by clinical and toxicological data into four groups: lead-poisoned (mean blood lead level: 74.5 μg/dL), and moderately (mean: 52.8), slightly (mean: 41 μg/dL), or physiologically (mean: 23 μg/dL) exposed to lead. The lead-poisoned group and moderately exposed groups had decreases in fertility, as measured by asthenospermia, hypospermia, and teratospermia. The effect of lead was thought to be directly on the testes, because tests for changes in gonadotropin secretion were negative. Secretion of androgens by the testes was not affected.

Wildt et al. (1983) compared two groups of men in a Swedish battery factory. The high-lead men had blood lead levels ≥50 μg/dL at least once prior to the study, and had mean blood lead levels of 46.1 and

44.6 μg/dL (range: 25 to 75 μg/dL) during fall and spring test periods. The controls (low-lead men) had blood lead levels that seldom exceeded 30 μg/dL and had mean blood lead levels of 31.1 and 21.5 μg/dL (range: 8 to 39 μg/dL) during fall and spring test periods. The high-lead group tended to exhibit decreased prostate/seminal vesicle function (as measured by seminal plasma constituents), low semen volumes, and lower functional maturity of sperm [as measured by swelling of the sperm heads in detergent (sodium dodecyl sulfate) solution]. Weaknesses of the study include the relatively high blood lead levels of the controls and current or past urogenital tract infections in some of the controls and in none of the high-lead men.

Studies of lead workers with higher blood lead levels (≥66 μg/dL) indicate that lead acts directly on the testes to produce severe depression of sperm count and peritubular testicular fibrosis, and also produces defects in regulation of LH secretion at the hypothalamic-pituitary level (Braumstein et al. 1978, Cullen et al. 1984)

Animal. Pertinent data regarding the reproductive toxicity of inhaled lead on animals were not located in the available literature.

4.3.4.2 Oral

Human. According to the EPA (1986a), lead was used in nostroms sold as abortifacients in Britain around the turn of the century. These preparations apparently were effective at levels which produced marked signs of lead poisoning in the women. The available studies were methodologically inadequate and did not provide dose-effect information.

A study of pregnancies in the lead smelter town (higher lead exposure) and environs (low lead exposure) of Port Pirie, South Australia, found that 22/23 miscarriages and 10/11 stillbirths in the study occurred in the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring in residents outside Port Pirie (McMichael et al. 1986). This study is discussed more fully in the section on developmental toxicity (4.3.3.2) because the primary focus of the study is the effects of prenatal lead exposure on fetal and early childhood development.

Animal. Hilderbrand et al. (1973) reported that oral dosing of female rats for 30 days with lead acetate at 5 and 100 μg/day Pb produced blood lead levels of 30 and 53 μg/dL, respectively. Irregular estrous cycles occurred at both treatment levels and ovarian follicular cysts with reductions in numbers of corpora lutea occurred at the higher level. Male rats treated orally with lead acetate in the same manner had blood lead levels of 19 and 30 μg/dL, respectively, and had testicular damage at the higher exposure level.

Chowdhury et al. (1984) found testicular atrophy and cellular degeneration in male rats given lead acetate in the drinking water at 1 g/L (1,000 ppm) for 60 days. Blood lead levels averaged 142.6 μg/dL. At a lower exposure level and mean blood lead level of 71.7 μg/dL, the seminiferous tubular diameter and spermatic count were reduced. No significant changes were seen at a blood lead level of 54.0 μg/dL.

Decreases in sperm motility and osmotic stability were reported to result from oral administration of 0.05 mg/kg of lead to male rats for 20 to 30 days in a study from the U.S.S.R. (Krasovskii et al. 1979). Blood lead data were not available.

Grant et al. (1980) reported delayed vaginal opening in rats that were exposed to 25, 50, or 250 ppm lead (as lead acetate) in the drinking water indirectly through their dams during gestation and lactation and then directly. Delayed vaginal opening occurred in the 25-ppm group in the absence of any growth retardation or other developmental delay; median blood lead levels were 18 to 29 μg/dL (at 1 to 2 months of age). This effect was not seen at 5 ppm (median blood lead levels: 9-16 μg/dL).

4.3.4.3 Dermal

Pertinent data regarding the reproductive toxicity of dermal exposure to lead in humans or animals were not located in the available literature.

4.3.4.4 General discussion

There is sufficient qualitative evidence to support the conclusion that at high exposure levels lead has significant adverse effects on human reproduction; however, the data do not permit any estimate of effect levels in women, and only a tentative conclusion that effects on sperm or the testes may result from chronic exposure at blood lead levels of 40 to 50 μg/dL in men. Nevertheless, EPA (1986a) does list a LOEL of 60 μg/dL for female reproductive effects even though they state that the data do not permit such an estimate. The basis for this LOEL is not apparent.

4.3.5 Genotoxicity

4.3.5.1 Human

Evaluation of the genotoxicity of lead in humans has focused on in vitro studies of structural chromosomal aberrations and sister chromatid exchange in cultures of lymphocytes taken from healthy individuals (Table 4.2), and evaluations of lymphocytes from occupationally or environmentally exposed persons (Table 4.3). Results of in vitro studies with human lymphocyte cultures, performed with lead acetate, were nearly equally divided between positive (Beek and Obe 1974, Stella et al. 1978, Niebuhr and Wulf 1984) and negative (Schmid et al. 1972, Beek and Obe 1975, Gasiorek and Bauchinger 1981, Deknudt and Deminatti 1978).

Results of in vivo tests are also contradictory, but do suggest that lead has an effect on chromosomes. Increased frequency of sister chromatid exchange was not observed in one study of occupationally exposed adults with blood lead levels of 48.7 μg/dL (Maki-Paakkanen et al. 1981) or in environmentally exposed children with blood lead levels of 30 to 63 μg/dL (Dalpra et al. 1983). Grandjean et al. (1983), however, reported increased frequency of sister chromatid exchange in lead-exposed workers and noted a tendency for increased frequency of sister chromatid exchange with increased duration of occupational exposure independent of blood lead level.

Table 4.2. Genotoxicity of lead in vitro

End point	Species (test system)	Results[a]		References
		With activation	Without activation	
Gene mutation or DNA modification	*Salmonella typhimurium* (reverse mutation); *Escherichia coli* (forward mutation, DNA modification); *Saccharomyces cerevisiae* (reverse mutation); *B. subtilis* (rec assay)	–	–	Bruce and Heddle 1979, Dunkel et al. 1984, Nestmann et al. 1979, Simmon 1979a, Rosenkranz and Poirer 1979, Kharab and Singh 1985, Fukunaga et al. 1982, Nishioka 1975
Gene conversion or mitotic recombination	*S. cerevisiae*	–	–	Kharab and Singh 1985, Fukunaga et al. 1982, Nestmann et al. 1979, Simmon 1979b
RNA or DNA synthesis	*E. coli* RNA polymerase or Avian myetoblastosis DNA polymerase	NA	+	Hoffman and Niyogi 1977, Sirover and Loeb 1976
Chromosomal aberration, DNA repair, mitotic disturbance	Chinese hamster ovary cells; Syrian hamster embryo cells	NA	+	Bauchinger and Schmid 1972, Costa et al. 1982, Robison et al. 1984
Structural chromosomal aberration	Human lymphocyte cultures	NA	Mixed	Beek and Obe 1974, Stella et al. 1978, Schmid et al. 1972, Gasiorek and Bauchinger 1981, Deknudt and Deminatti 1978
Sister chromatid exchange	Human lymphocyte cultures	NA	Mixed	Beek and Obe 1975, Niebuhr and Wulf 1984

[a] + = largely positive; - = negative; mixed = approximately equivalent numbers of positive and negative results; NA = not applicable.

Table 4.3. Genotoxicity of lead in vivo

End point	Species (test system)	Blood lead levels[a] (μg/dL)	Results[b]	References
Chromosome loss or nondisjunction	*Drosophila melanogaster*	NA	−	Ramel and Magnusson 1979
Structural chromosomal aberrations or gaps, micronucleus formation, unscheduled DNA synthesis, sister chromatid exchange	Mouse bone marrow, rat bone marrow, mouse leukocyte, monkey lymphocyte, rabbit	NR	Mixed	Jacquet et al. 1977, Jacquet and Tachon 1981, Tachi et al. 1985, Muro and Goyer 1969, Choie and Richter 1978, Willems et al. 1982, Bruce and Heddle 1979, Deknudt et al. 1977, Deknudt and Gerber 1979
Chromosomal aberration	Human, occupational	22–120	Mixed	O'Riordan and Evans 1974, Bulsma and DeFrance 1976, Bauchinger et al. 1977, Schmid et al. 1972, Mäki-Paakkanen et al. 1981, Schwanitz et al. 1970–1975, Al-Hakkak et al. 1986, Forni et al. 1976, Nordenson et al. 1978
Sister chromatid exchange	Human, occupational exposure	29–75	−	Grandjean et al. 1983, Mäki-Paakkanen et al. 1981
	Human, environmentally exposed children	30–63	−	Dalpra et al. 1983
Effects on cell division	Human	40–100	+	Forni et al. 1976, Bulsma and DeFrance 1976, Sarto et al. 1978, Schwanitz et al. 1970

[a]NA = not applicable; NR = not reported.
[b]+ = largely positive; - = negative; mixed = approximately equivalent numbers of positive and negative results.

Occupational exposure or voluntary ingestion of lead is associated with increased mitotic activity in peripheral lymphocytes (Bulsma and DeFrance 1976), increased rate of abnormal mitosis (Schwanitz et al. 1970; Forni et al. 1976, 1980; Sarto et al. 1978), and increased incidence of chromosomal aberrations (Al-Hakkak et al. 1986; Forni et al. 1976, 1980; Schwanitz et al. 1970; Nordenson et al. 1978) at blood lead levels ranging from 22 to 89 μg/dL. Nordenson et al. (1978) reported a correlation between blood lead levels and the frequency of chromosomal aberrations. Other investigators, however, reported no increase in the frequency of chromosomal aberrations in occupationally exposed workers with blood lead levels ranging from 38 to 120 μg/dL (O'Riordan and Evans 1974, Bulsma and DeFrance 1976, Bauchinger et al. 1977, Schmid et al. 1972, Maki-Paakkanen et al. 1981, Schwanitz et al. 1975) or in environmentally exposed children with blood lead levels of 12 to 33 μg/dL (Bauchinger et al. 1977).

In studies with organolead compounds, trimethyl and triethyl lead were associated with increased frequency of induced sister chromatid exchanges (Grandjean and Andersen 1982, Niebuhr and Wulf 1984) and altered chromosome length (an indication of mitotic spindle function) in cultured human lymphocytes (Grandjean and Andersen 1982).

4.3.5.2 Nonhuman

Tests for gene mutations, DNA modification, and recombinations in various microorganisms (see Table 4.2) using lead acetate (Nishioka 1975; Bruce and Heddle 1979; Dunkel et al. 1984; Simmon 1979a,b; Simmon et al. 1979; Rosenkranz and Poirer 1979), lead nitrate (Kharab and Singh 1985) and lead chloride (Fukunaga et al. 1982, Nishioka 1975) were consistently negative with or without metabolic activation. A positive response was observed by Nestmann et al. (1979) for lead chromate, but further testing clarified that the positive response was associated with the chromate rather than the lead moiety. Lead chloride has been shown to inhibit both RNA (Hoffman and Niyogi 1977) and DNA (Sirover and Loeb 1976) synthesis.

In mammalian test systems in vitro (Syrian or Chinese hamster cells), lead acetate gave conflicting results for structural chromosomal aberrations (Robison et al. 1984, Bauchinger and Schmid 1972). Lead acetate increased the frequency of DNA repair (Robison et al. 1984), the frequency of achromatic lesions and gaps (Bauchinger and Schmid 1972), and both lead acetate (Bauchinger and Schmid 1972) and lead sulfate (Costa et al. 1982) interfered with normal mitotic division.

In in vivo tests (see Table 4.3) lead nitrate was negative for chromosome loss and nondisjunction in *Drosophila melanogaster* (Ramel and Magnusson 1979). Results were mixed for various manifestations of genotoxicity in several experiments with lead acetate in mammals (Jacquet et al. 1977, Jacquet and Tachon 1981, Tachi et al. 1985, Muro and Goyer 1969, Choie and Richter 1978, Willems et al. 1982, Bruce and Heddle 1979, Deknudt et al. 1977, Deknudt and Gerber 1979).

Genotoxicity testing of organolead compounds yielded mixed results. Tetramethyl lead was negative in plate tests in *S. typhimurium* with and without metabolic activation (Haworth et al. 1983), and triethyl lead was positive for nondisjunction and gave conflicting results for

chromosome loss in *D. melanogaster* (Ahlberg et al. 1972, Ramel 1973, Ramel and Magnusson 1979).

4.3.5.3 General discussion

The EPA (1986a) noted that lead was consistently negative in tests for mutagenicity in microbial systems and concluded that these systems are not sufficiently developed to demonstrate mutagenicity for metals that are known carcinogens. The EPA (1986a) also noted that conflicting results were reported for genotoxicity in mammalian (including human) tests in vitro and in vivo, although the weight of evidence suggests a clastogenic effect of lead. It was hypothesized that increasing the length of culture time (i.e., from 48 to 72 h) may improve the likelihood of a positive result (EPA 1986a). In addition, the status of calcium nutrition may be important in the expression of lead-induced clastogenicity in both in vitro and in vivo tests. Studies in mice (Deknudt and Gerber 1979) and monkeys (Deknudt et al. 1977) indicated that calcium deficiency may enhance the genotoxicity of lead as it does other manifestations of lead toxicity.

4.3.6 Carcinogenicity

4.3.6.1 Inhalation

Human. Several studies reviewed by the EPA (1986a) have examined the association of occupational exposure to lead with increased cancer risk. Generally, these studies are limited in usefulness because the actual compound(s) of lead, the route(s) of exposure, and levels of lead to which the workers were exposed were not reported. Furthermore, exposure to other chemicals including arsenic probably occurred, particularly in lead smelters, and smoking was a possible confounder (Cooper 1976, EPA 1988a, IARC 1987). These studies, therefore, are not sufficient to evaluate the carcinogenicity of lead in humans and this report is restricted to the most comprehensive of these studies.

The most extensive was a series of reports of a large number of workers at six domestic lead production plants (smelters and recycling plants) and ten battery plants (Cooper and Gaffey 1975, Cooper 1976). Increased incidences of total malignant neoplasms were observed for both categories of lead workers, but the increase was statistically significant only for lead production workers. The increase in total malignancies appeared to be due to small but statistically nonsignificant increases in digestive and respiratory tract tumors, evident in both the lead production and battery workers, and in urinary tract tumors in production workers. In a statistical reanalysis of the Cooper and Gaffey (1975) data, Kang et al. (1980) determined that the incidence of total malignant neoplasms, cancers of the digestive tract, and cancers of the respiratory tract were statistically elevated in both lead production workers and battery workers.

In a follow-up to the original study, Cooper (1981) reported that lead had no cancer-inducing properties, although SMRs of 125 to 149% for total malignant neoplasms, 172% for respiratory cancer, and 229% for cancers of other sites were reported in battery workers. In a recent evaluation of a more select subset from the original study, Cooper et

al. (1985) reported increased SMRs for total malignancies in both groups of workers (statistically significant only in the battery workers because of the statistical power of the larger numbers in this group) attributed to digestive and respiratory cancers.

Selevan et al. (1985) reported an SMR of 204% for mortality from renal cancer in a cohort of lead smelter workers. Although the results were not statistically significant because of small numbers, the study is of interest because animal studies associate lead exposure with kidney cancer (Sect. 4.3.6.2 on carcinogenicity after oral exposure). In addition, two cases of renal cancer have been reported in occupationally exposed men who had symptoms of lead poisoning and high blood lead levels (Baker et al. 1980, Lilis 1981). In one case, the tumor was reported to contain a high level of lead and to have histopathological characteristics similar to those of kidney tumors induced by lead in animals (Baker et al. 1980).

Animal. Pertinent data were not located regarding the carcinogenicity of lead in animals exposed by inhalation.

4.3.6.2 Oral

Human. Pertinent data were not located regarding the carcinogenicity of lead in humans exposed solely by the oral route.

Animal. Several studies in animals reviewed by the the EPA (1986a) qualitatively associate oral exposure to several different lead compounds with renal tumors in various species of animals. Most studies were conducted with one or two dosages of lead. Some examples are summarized in Table 4.4. Renal tumors were often observed at dosages lower than those associated with mortality attributed to renal damage.

The most comprehensive set of studies was performed by Azar et al. (1973), who administered lead acetate to rats at nominal concentrations of 0, 10, 50, 100, 500, 1,000, or 2,000 ppm lead in the diet for 2 years. The control group consisted of 100 rats per sex, and the 10- to 500-ppm treatment groups had 50 rats per sex. After the study was in progress for a few months, groups of 20 rats per sex were fed diets containing 0, 1,000, or 2,000 ppm. Blood lead levels, measured at termination after 24 months of exposure were 12.7, 11.0, 18.5, 35.2, and 77.8 μg/dL in the 0-, 10-, 50-, 100-, and 500-ppm groups; and 16.4, 98.6, and 98.4 μg/dL in the 0-, 1,000-, and 2,000-ppm groups, respectively. Renal tumors occurred in 5/50 male rats at 500 ppm, in 10/20 males at 1,000 ppm, and in 16/20 males and 7/20 females at 2,000 ppm.

4.3.6.3 Dermal

Human. Data regarding the carcinogenicity of lead in dermally exposed humans were not located in the available literature.

Animal. Baldwin et al. (1964) reported renal tumors in 5/59 mice in a skin painting experiment in which lead naphthenate in benzene was applied 1 or 2 times weekly for 18 months. There was no effect on the incidence of skin tumors. Benzene-treated controls were not maintained.

Table 4.4. Examples of studies on the incidence of tumors in experimental animals orally exposed to lead compounds

Species	Pb compound	Dose and mode	Incidence (any type) of neoplasms	References
Rat	Pb acetate	1% (in diet)	15/16 (kidney tumors) 14/16 (renal carcinomas)	Boyland et al. 1962
Rat	Pb subacetate	0.1% and 1.0% (in diet)	11/32 (renal tumors) 13/24 (renal tumors)	Van Esch et al. 1962
Rat	Pb subacetate	0.5-1% (in diet)	14/24 (renal tumors)	Haas et al. 1967
Rat	Pb subacetate	1% (in diet)	31/40 (renal tumors)	Mao and Molnar 1967
Rat	Pb acetate	3 mg/day for 2 months; 4 mg/day for 16 months (*per os*)	72/126 (renal tumors) 23/94 males [testicular (Leydig cell) tumors]	Zawirska and Medras' 1968
Hamster	Pb subacetate	1.0 and 0.5% (in diet)	No significant incidence of renal neoplasms	Van Esch and Kroes 1969
Mouse	Pb subacetate	0.1 and 1.0% (in diet)	7/25 (renal carcinomas) at 0.1%; substantial death at 1.0%	Van Esch and Kroes 1969
Rat	Pb nitrate	25 g/L (in drinking water)	No significant incidence of tumors	Schroeder et al. 1970
Rat	Pb acetate	3 mg/day (*per os*)	89/94 (renal, pituitary, cerebral gliomas, adrenal, thyroid, prostatic, mammary tumors)	Zawirska and Medras' 1972
Rat	Pb acetate	0, 10, 50, 100, 500, 1,000, 2,000 ppm (in diet) for 2 years	No tumors 0-100 ppm; 5/50 (renal tumors) at 500 ppm; 10/20 at 1,000 ppm; 16/20 males, 7/20 females at 2,000 ppm	Azar et al. 1973
Rat	Pb acetate	0, 26, 2,600 ppm (in drinking water for 76 weeks)	81% (renal tumors) at 2,600 ppm	Koller et al. 1985

4.3.6.4 Other tests

Lead subacetate was positive at high dosages in the strain A mouse lung adenoma bioassay (Stoner et al. 1976, Poirier et al. 1984), but the positive response was blocked by simultaneous administration of calcium or magnesium acetate (Poirier et al. 1984). Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Zollinger 1953, Balo et al. 1965). Lead acetate was positive in cell transformation tests in Syrian hamster embryo cells (Pienta et al. 1977, Dunkel et al. 1981) and in MLV-infected rat embryo cells (Dunkel et al. 1981), and enhanced simian adenovirus (SA-7) transformation of Syrian hamster embryo cells (Casto et al. 1979). Lead oxide also enhanced SA-7 transformation of Syrian hamster embryo cells (Casto et al. 1979).

4.3.6.5 General discussion

According to a recent EPA (1988a) assessment, the available epidemiological studies lacked quantitative exposure data for lead and for possible confounding exposures (e.g., arsenic, smoking), cancer excesses in the lung and stomach of lead-exposed workers were relatively small, dose-response relationships were not demonstrated in any study, and no consistency of site was observed among the various studies. The EPA (1988a) concluded that the human data are inadequate to refute or demonstrate the potential carcinogenicity of lead exposure for humans.

The EPA (1988a) concluded that the animal data are sufficient to demonstrate that lead and (inorganic lead) compounds, particularly soluble lead salts, are carcinogenic to animals. Although dose-response data are available from animal studies, the EPA (1988a) recommended that a numerical estimate of cancer potency or risk based on such data should not be used because of the uncertainties, some of which may be unique to lead, involved in such an extrapolation. Current knowledge of the pharmacokinetics of lead indicates that an estimate derived by standard methods would not adequately delineate the potential risk (EPA 1988a). EPA (1988a) assigned lead and (inorganic) lead compounds a classification of B2 - probable human carcinogen.

IARC (1987) concluded that the evidence for carcinogenicity of lead and inorganic lead compounds was inadequate in humans and sufficient in animals. IARC (1987) classified lead and inorganic lead compounds in IARC Group 2B - possible human carcinogen.

4.4 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetic and toxicological behavior of lead can be affected by interactions with essential elements and nutrients. In humans, the interactive behavior of lead and various nutritional factors is appropriately viewed as particularly significant for children, since this age group is not only particularly sensitive to the effects of lead, but also experiences the greatest changes in relative nutrient status.

Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. Ziegler et al. (1978) observed that lead retention in infants was inversely correlated

with calcium intake, expressed either as a percentage of total or on a weight basis. Mahaffey et al. (1976) showed that children 1 to 4 years of age with blood lead levels >40 μg/dL had significantly lower intake of phosphorus and calcium compared with a control group, while iron intake in the two groups was comparable. Using adults, Heard and Chamberlain (1982) monitored the uptake of ^{203}Pb from the gut in eight subjects as a function of the amounts of dietary calcium and phosphorus. Without supplementation of these minerals in fasting subjects, the label absorption rate was ~60%, compared with 10% in subjects supplemented with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium alone reduced uptake by a factor of 1.3 and phosphorus alone by 1.2; both together yielded a reduction factor of 6. Sorrell et al. (1977) found that blood lead content was inversely correlated with calcium intake in children 1 to 4 years of age. Children with blood levels >60 μg/dL had significantly ($P < 0.001$) lower intakes of calcium and vitamin D.

Rosen et al. (1980, 1981) found that children with elevated blood lead (33 to 120 μg/dL) had significantly lower serum concentrations of the vitamin D metabolite 1,25-dihydroxyvitamin D compared with age-matched controls ($P < 0.001$), and showed a negative correlation of serum 1,25-dihydroxyvitamin D with lead over the range of blood lead levels measured.

Johnson and Tenuta (1979) determined that calcium intake was negatively correlated with blood lead in 43 children aged 1 to 6 years. The high lead group also consumed less zinc than children with lower blood levels. In a group of 13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children. Chelation therapy reduced the mean level even further. Chisolm (1981) reported an inverse relationship between ALA in urine and the amount of chelatable or systemically active zinc in 66 children challenged with EDTA and having blood lead levels ranging from 45 to 60 μg/dL. Thomasino et al. (1977) described a case of a lead-intoxicated man who was given calcium sodium EDTA and zinc sulfate therapy. During chelation therapy, blood lead and erythrocyte ALA-D activity decreased and urinary excretion of zinc increased. Chelation therapy followed by treatment with zinc sulfate increased ALA-D activity. Boscolo et al. (1983a,b) found that combined treatment of lead-exposed patients with EDTA and zinc resulted in lowered blood pressure, elevated erythrocyte ALA-D activity, decreased urinary excretion of ALA, ameliorated heme synthesis and prevented zinc depletion. These results suggest that zinc plays a protective role in lead toxicity.

Yip et al. (1981) found that 43 children with elevated blood lead (>30 μg/dL) and EP (>35 μg/dL) had an increased prevalence of iron deficiency as these two parameters increased. Chisolm (1981) demonstrated an inverse relationship between chelatable iron and chelatable body lead levels as indexed by urinary ALA levels in 66 children with elevated blood lead. Watson et al. (1980) reported that adult subjects who were iron deficient showed a lead absorption rate 2 to 3 times greater than subjects who were iron replete. Daily nutritional intake of dietary fiber, iron, and thiamine were negatively correlated with blood lead levels in male workers occupationally exposed

to lead in a steel factory (Ito et al. 1987). Davis and Avram (1978) found a significant reversal of in vitro inhibitory effects of lead on human ALA-D activity by low concentrations of cadmium or zinc.

Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. These interaction studies are summarized in Table 4.5.

Lead has also been found to interact with a number of other metals in the bodies of animals with resultant synergistic, additive, or antagonistic effects.

Animals on low-calcium diets exhibit increased susceptibility to lead as a consequence of increased lead retention associated with decreased renal excretion of lead (Goyer 1986). A low-calcium diet has been shown to promote genetic damage by lead (Deknudt and Gerber 1979). Lead administered to mice in combination with a low-calcium diet produced an excess of chromosomal aberrations compared with low-calcium controls fed no lead or with mice administered lead on a normal-calcium diet. Deknudt et al. (1977) also found that the frequency of severe chromosomal abnormalities was significantly increased in monkeys given lead in conjunction with a low-calcium diet compared with a group given as much lead but on a normal diet. Poirier et al. (1984) found that calcium and magnesium prevented an increase in lung adenoma formation in mice administered lead subacetate.

Cadmium also affects the toxicity of lead. Anca et al. (1982) reported that rats given lead and cadmium in combination exhibited increased body weight loss and increased relative brain, liver, and adrenal weights compared with animals that were given either lead or cadmium alone. Toxic effects of the kidney, liver, and hematopoietic system due to the combined action of lead and cadmium were also reported (Salangina et al. 1982). A synergistic effect of these metals was found on prostatic cytology and testicular damage in male rats (Fahim and Khare 1980). Suzuki (1981) reported that cadmium inhibited the retention of lead or increased its excretion, but lead did not affect the accumulation of cadmium. Suzuki (1981) also reported simple additive effects of lead and cadmium on the growth of rats. Rats fed lead and cadmium had a marked reduction of reticulocytosis compared with rats fed lead alone (Thawley et al. 1977).

Several interactions of lead and iron have been reported. Iron appeared to reduce the effects of orally or subcutaneously administered lead on blood enzyme and liver catalase activity (Bota et al. 1982). Treatment of pregnant hamsters with iron- or calcium-deficient diets in conjunction with orally administered lead resulted in embryonic or fetal mortality and abnormalities (runting, edema) in the litters, while treatment with complete diets and lead did not (Carpenter 1982). In addition, Makarov and Isakhanov (1981) suggested that iron deficiency was probably the cause of embyrotoxicity in lead-treated rats. Inadequate levels of iron in association with increased body burdens of lead enhanced biochemical changes associated with lead intoxication (Dhir et al. 1985). Ferrous iron was reported to protect against the

Table 4.5. Effect of nutritional factors on lead uptake in animals

Factor	Species	Index of effect	Interactive effect	References
Calcium	Rat	Lead in tissues and severity of effect at low levels of dietary calcium	Low dietary calcium (0.1%) increases lead absorption and severity of effects	Six and Goyer 1970, Mahaffey et al. 1973
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al. 1975
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al. 1972
Calcium	Lamb	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al. 1977
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al. 1978a
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Six and Goyer 1972
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al. 1978b
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton 1978
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al. 1978
Protein	Rat	Tissue levels of lead	Casein diet increases lead uptake compared to soybean meal	Anders et al. 1982
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett 1981
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca 1981
Zinc	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes 1976, El-Gazzar et al. 1978
Zinc	Rat	Lead transfer in utero and in milk during lactation	Low-zinc diet of mother increases lead transfer in utero and in maternal milk	Cerklewski 1979

Table 4.5. (continued)

Factor	Species	Index of effect	Interactive effect	References
Zinc	Rat	Tissue retention	Low zinc diet enhances brain Pb levels	Bushnell and Levin 1983
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder et al. 1973, Klauder and Petering 1975
Iron	Rat	In utero or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both in utero and milk transfer of lead to sucklings	Cerklewski 1980
Phosphorus	Rat	Lead uptake in tissues	Reduced phosphorus increases ^{203}Pb uptake 2.7-fold	Barltrop and Khoo 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances both lead retention and lead deposition in bone	Barton and Conrad 1981
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead absorption	Smith et al. 1978
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al. 1980
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40% enhance lead absorption	Barltrop and Khoo 1975
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increases lead absorption	Barltrop and Khoo 1975

inhibition of hemoglobin synthesis and cell metabolism by lead (Waxman and Rabinovitz 1966, Dhir et al. 1985). In addition, the incorporation of iron into heme in the mouse embryonic liver was greatly decreased in lead-treated mice, resulting in retarded embryo growth due to impaired heme synthesis (Gerber and Maes 1978).

The reduction in uptake of lead and decrease of lead-induced ALA-D inhibition upon administration of copper may be achieved through a competition between the two metals for binding to proteins (Edshall and Wyman 1958, Underwood 1977). A study by Cho and Cha (1982) found that the content of both iron and lead in the blood were higher in rats given lead alone than in rats administered lead plus copper and that blood ALA-D was reduced further in the lead-plus-copper groups than the group receiving lead alone.

Zinc may have a protective effect against lead toxicity. Goyer (1986) reported that zinc added in the diet has been found to protect horses grazing on lead-contaminated pastures from clinical signs of lead toxicity. Haeger-Aronsen et al. (1976) reported that zinc almost entirely eliminated the inhibition of ALA-D by lead, and speculated that the prevention of the development of pharyngeal and laryngeal paralysis seen in lead-intoxicated foals (Willoughby et al. 1972) may be due to zinc's antagonistic effects upon ALA-D. Brewer et al. (1985) noted that zinc protected horses and rats against the effects of orally administered lead. Brewer et al. (1985) suggested that zinc probably acts via an intestinal metallothionein mechanism, and that supplementation with zinc sufficient to induce significant intestinal metallothionein (which binds lead) could be used to reduce the toxicity of lead. A protective effect of zinc against lead toxicity in the chick embryo has also been shown (Srivastava and Tandon 1984).

Evidence suggests that lead increases the toxic effects of mercury. Singh and Sivalingam (1982) reported that the addition of lead to mercury increased the inhibitory effects of mercury on catalase activity in vitro in the fish, *Sarotherodon mossambicus*. In the rat, the administration of lead nitrate increased kidney and liver glutathione content and resulted in increased mercury deposition in the kidney, along with increased lethality (Congiu et al. 1979).

The interaction of lead and ethanol has been studied by Flora and Tandon (1987), who suggested that rats exposed to lead and ethanol are more susceptible to the neurological and hepatotoxic effects of lead. In this study, the simultaneous exposure of rats to lead and ethanol resulted in a significantly higher concentration of lead in blood, brain, and liver tissues compared with rats treated with lead alone. Lead given with ethanol resulted in more pronounced inhibition of the activities of hepatic glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) than did treatment with lead by itself. In addition, exposure to lead plus ethanol resulted in a greater depression of dopamine and 5-hydroxytryptamine levels in the rat brain than did lead treatment alone.

Gelman et al. (1978) found that the interaction between lead and phenylhydrazine produced an additive effect in the acute hemolytic phase of anemia and a probable synergistic effect during the compensatory phase of anemia.

5. MANUFACTURE, IMPORT, USE, AND DISPOSAL

5.1 OVERVIEW

Almost all lead-producing mines in the United States are underground operations. As of 1983, there were 39 lead mines in operation in the United States. The nation's largest lead refineries are located in southeastern Missouri where eight mines provide ~91% of the total domestic output of lead ore. During 1986, U.S. production of refined lead from primary sources (ore and base bullion) was 808 million lb, and production of lead from secondary sources (old scrap and product wastes) was 1,356 million lb. Lead is used primarily in the production of storage batteries, oxides, and chemicals (including gasoline additives), and ammunition and various metal products (i.e., sheet lead, solder, and pipes). The primary method of disposal for lead is recycling. Recycling of old scrap metal supplies ~45% of the U.S. demand for lead. However, a large amount of lead is disposed of annually in municipal and hazardous waste landfills.

5.2 PRODUCTION

As mentioned above, almost all lead-producing mines in the United States are underground operations. Lead obtained as a by-product from open-pit copper mines is the only source of aboveground lead production. Mined ore is crushed, ground, and concentrated (most commonly by flotation). Treatment of lead concentrate involves sintering, smelting, drossing, and refining to 99.5 to 99.99% purity (Woodbury 1985a). Lead can also be recovered from secondary sources, which include scrap, product wastes, refinery drosses, and residues (USDI 1987). Detailed descriptions of the mining, milling, smelting, and refining processes, and processes for recovery from secondary sources are reported in Howe (1981).

During 1986, mine production of recoverable lead in the United States was 749 million lb, production of refined lead from primary sources was 808 million lb, and production of lead by recovery from secondary sources was 1,356 million lb (USDI 1987). Consumption of lead in the United States during 1986 was 2,480 million lb (USDI 1987).

During 1983, the domestic lead mining industry was composed of 39 mines distributed between 8 states. Eight mines in southeastern Missouri produced 91% of the total domestic output in 1983, while a total of 23 mines in Idaho, Colorado, Montana, and New York accounted for ~9% of the domestic output (Woodbury 1985a). The nation's largest refineries of lead from primary sources are located in southeastern Missouri (Woodbury 1985b). As of 1988, the U.S. secondary lead industry consisted of 20 companies, which operated 27 plants with metal-refining capacities ranging from ~5,000 to 100,000 tons per year, representing 96% of the

total secondary lead production in the United States. Twenty-three small producers at 24 plants with annual capacities of 1,000 tons per year or less accounted for the remaining 4% of secondary lead production. The U.S. secondary production of lead was 737,000 metric tons in 1988, ~87% of the production capacity (Woodbury 1989).

5.3 IMPORT

During 1986, 319 million lb of lead was imported for consumption in the United States (USDI 1987).

5.4 USES

The domestic use pattern for lead in 1986 was as follows (USDI 1987): storage batteries, including oxides, 75.9%; other oxides and chemicals, including gasoline additives, 8.7%; ammunition, 4.0%; miscellaneous metal products, including sheet lead, solder, pipes, traps, and other extruded products, cable covering, and other metal products, 9.0%; miscellaneous uses, 2.4%. The commercial importance of lead is based on its ease of casting, high density, low melting point, low strength, ease of fabrication, acid resistance, electrochemical reaction with sulfuric acid, and chemical stability in air, water, and soil (Howe 1981). In recent years, the amounts of lead used in paints and ceramic product applications, in gasoline additives and in solder, particularly in applications involving potable water supplies and food containers, have been reduced because of adverse health effects (Woodbury 1985a,b).

5.5 DISPOSAL

The primary method of handling the disposal of lead is recycling. An estimated 70 to 75% of the consumed lead in the United States is considered to be recyclable. Certain applications of lead preclude recycling (i.e., use as a gasoline additive). Recycling of old scrap metal supplies ~45% of the U.S. demand for lead (Woodbury 1985a).

A large amount of lead is disposed of annually in municipal and hazardous waste landfills. Lead is commonly disposed of as part of both domestic and commercial lead-containing products (Perwak et al. 1982). Lead-containing waste products include storage batteries, ammunition waste, sheet lead, solder, pipes, traps, and other metal products; solid waste and tailings from lead mining; items covered with lead-based paint; and solid wastes created by mineral ore processing, iron and steel production, copper and zinc smelting, and the production and use of various lead-containing products (Perwak et al. 1982, USDI 1987).

6. ENVIRONMENTAL FATE

6.1 OVERVIEW

The primary source of lead in the environment is anthropogenic emissions to the atmosphere. As of 1984, gasoline combustion was responsible for ~90% of all anthropogenic lead emissions; however, EPA has been phasing out the use of lead alkyls in gasoline, and auto emissions are no longer the single largest source of lead in the atmosphere. Atmospheric deposition is the largest source of lead found in both soils and surface waters. Lead is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for lead. Lead particles are removed from the atmosphere primarily by wet and dry deposition. The average residence time is expected to range between 7 and 30 days. Over this time, long distance transport, up to thousands of kilometers, may take place. Lead is extremely persistent in both water and soil. The speciation of lead in these media varies widely depending upon such factors as temperature, pH, and the presence of humic materials. Lead is largely associated with suspended solids and sediments in aquatic systems, and it occurs in relatively immobile forms in soil.

6.2 RELEASE TO THE ENVIRONMENT

Lead is a naturally occurring element that has been found in the earth's crust and in all compartments of the biosphere. Both natural and anthropogenic processes are responsible for the distribution of lead throughout the environment. Of particular importance are emissions of lead to the atmosphere, which is the initial recipient for much of the lead dispersed throughout the environment. Estimated atmospheric emissions of lead from anthropogenic point and nonpoint sources in the United States during 1984 are listed in Table 6.1. Mobile and stationary sources of lead, although found throughout the nation, tend to be concentrated in areas of high population density and near smelters. Natural emissions of lead to the atmosphere from volcanoes and windblown dust are believed to be of minor importance (EPA 1986a).

As indicated in Table 6.1, automotive emissions have been the largest source of lead emitted to the atmosphere. More than 90% (mass basis) of automotive lead emissions are in the form of inorganic particulate matter (e.g., PbBrCl) and <10% (mass basis) is in the form of organolead vapors (e.g., lead alkyls). Because of a decrease in the lead content in unleaded gasoline and an increase in the number of cars that use unleaded gasoline, the amount of lead emitted to the atmosphere in the United States has been reduced substantially in recent years. The estimated lead emission from automobiles in 1984 was based on an average

Table 6.1. Estimated anthropogenic lead emissions to the atmosphere for the United States, 1984

Source category	Annual (1984) emissions (tons/year)	Percentage of total U.S. emissions
Gasoline combustion	34,881[a]	89.4
Waste oil combustion	781	2.0
Solid waste combustion	352[b]	0.9
Coal combustion	265	0.7
Oil combustion	115	0.3
Gray iron production	54	0.1
Iron and steel production	427	1.1
Secondary lead smelting	278	0.7
Primary copper smelting	29	0.1
Ore crushing and grinding	116	0.3
Primary lead smelting	1,150	2.8
Zinc smelting	116	0.3
Other metallurgical	11	0.1
Lead alkyl manufacture	224	0.6
Lead acid battery manufacture	112	0.3
Portland cement production	70	0.2
Miscellaneous	35	0.1
Total	39,016[c]	100%

[a]The estimated 1988 emissions from leaded gasoline (10×10^9 gal/year $\times$ 0.1 g Pb/gal) is about 1,100 tons/year.

[b]Because of the decrease in emissions from leaded gasoline (see footnote a) and an increase in municiple waste combustion since 1984, waste incineration probably accounts for larger amounts of release than either gasoline combustion or primary lead smelting.

[c]Inventory does not include emissions from exhausting workroom air, burning of lead-painted surfaces, welding of lead-painted steel structures, or weathering of painted surfaces.

Source: EPA 1986a.

content of 0.44 g/gallon gasoline (EPA 1986a); however, the current allowable lead content of leaded gasoline is 0.1 g/gallon gasoline (EPA 1985b). Based on this figure, estimated 1988 emissions from leaded gasoline is ~1,100 tons/year. This suggests that automotive emissions are no longer the single largest source of lead in the atmosphere.

No data are available on the amount of lead released to the environment from lead-based paints. Releases from lead-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of lead in air and on exposed surfaces. In some soils, deterioration and removal of lead-based paint from painted surfaces are the primary sources of lead (EPA 1986a).

The largest volume of organolead vapors released to the atmosphere results from the manufacture, transport, and handling of leaded gasoline. Such vapors are photoreactive, and their presence in local atmospheres is transitory. Organolead vapors have been found to contribute <10% of the total lead present in the atmosphere. Organolead vapors are most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, and parking garages) (EPA 1986a).

Second to atmospheric emissions, lead in the form of solid waste is the next largest source of lead released to the environment. Solid wastes are produced primarily as a result of domestic ore production and ammunition use. Other sources include solder, weights and ballasts, bearing metals, and iron and steel production. These sources are concentrated primarily in landfills. Levels of lead found in most other soils largely reflect atmospheric deposition patterns (Perwak et al. 1982).

Aquatic discharges resulting from major uses of lead are assumed to be small. Of the known aquatic releases, the largest ones are steel and iron industries and lead production (Perwak et al. 1982). Urban runoff and atmospheric deposition appear to be the major sources of lead found in the aquatic environment (Perwak et al. 1982, EPA 1986a).

6.3 ENVIRONMENTAL FATE

6.3.1 Air

In the atmosphere, lead exists primarily in the particulate form. Upon release to the atmosphere, lead particles are dispersed, transformed by physical and/or chemical processes, and ultimately removed from the atmosphere by wet or dry deposition. An important factor in determining the atmospheric transport of lead is particle size distribution. Large particles, particularly those with aerodynamic diameters >2 μm, settle out of the atmosphere fairly rapidly and are deposited relatively close to emission sources, whereas smaller particles may be transported thousands of kilometers. The dry deposition velocity for lead particles with aerodynamic diameters of 0.6 to 2.0 μm was estimated to range between 0.2 and 0.5 cm/s. The amount of lead scavenged from the atmosphere by wet deposition varies widely; wet deposition can account for 20 to 80% of lead deposition depending on such factors as geographic location and amount of emissions in the area

(NSF 1977, EPA 1986a). Larger amounts of lead are expected to be removed by wet deposition in areas of acid rain (e.g., northeastern United States), because acid rain has a tendency to solubilize lead (McDonald 1985). The average residence time of lead particles in the atmosphere is expected to range between 7 and 30 days (EPA 1986a).

Information available regarding the chemistry of lead in air is limited. Lead particles are emitted to the atmosphere from automobiles as lead halides (e.g., PbBrCl) and as double salts with ammonium halides (e.g., 2PbBrCl NH_4Cl); lead particles are emitted from mines and smelters primarily in the form of $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (EPA 1986a). In the atmosphere, lead exists primarily in the form of $PbSO_4$, $PbCO_3$, and 2PbBrCl NH_4Cl (NSF 1977). It is not completely clear how the chemical composition of lead changes during dispersion (EPA 1986a, NSF 1977).

Based on the vapor pressure of tetraethyl and tetramethyl lead, these two compounds are expected to exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). When exposed to sunlight, they decompose rapidly to trialkyl and dialkyl lead compounds by a combination of direct photolysis, reaction with hydroxyl radicals, and reaction with ozone. The half-life of tetraethyl lead in brightly sunlit atmospheres is expected to be ~1 h, while the half-life for tetramethyl lead will be on the order of several hours. Trialkyl compounds are expected to occur almost entirely in the vapor phase, whereas dialkyl compounds are expected to occur almost entirely in particulate form. Because of the relatively high water solubility of trialkyl and dialkyl lead compounds, washout is probably a major process for these compounds. In addition, the latter species may be significantly removed by dry deposition. Adsorption of tetraethyl and tetramethyl lead to atmospheric particles is not expected to be an important environmental sink (EPA 1985a, DeJonghe and Adams 1986).

6.3.2 Water

The chemistry of lead in aqueous solution is highly complex because this element can be found in a multiplicity of forms. Lead has a tendency to form compounds of low solubility with the major anions of natural water. In the natural environment, the divalent form (Pb^{2+}) is the stable ionic species of lead. Hydroxide, carbonate, sulfide, and, more rarely, sulfate may act as solubility controls in precipitating lead from water (Callahan et al. 1979). Tetraalkyl leads may also form by a combination of chemical/biological alkylation of inorganic lead compounds under appropriate conditions (EPA 1985a).

The amount of lead that remains in solution depends upon the pH of the water and the dissolved salt content. Equilibrium calculations show that at pH >5.4, the total solubility of lead is ~30 µg/L in hard water and ~500 µg/L in soft water. Sulfate ions, if present in soft water, limit the lead concentration in solution through the formation of lead sulfate. Above pH 5.4, $PbCO_3$ and $Pb_2(OH)_2CO_3$ limit the concentration. The carbonate concentration is in turn dependent upon the partial pressure of CO_2, pH, and temperature (EPA 1986a).

A significant fraction of lead carried by river water is expected to be in an undissolved form, which can consist of colloidal particles or larger undissolved particles of lead carbonate, lead oxide, lead hydroxide, or other lead compounds incorporated in other components of surface particulate matters from runoff. Lead may occur either as sorbed ions or surface coatings on sediment mineral particles, or it may be carried as a part of suspended living or nonliving organic matter in water. The ratio of lead in suspended solids to lead in dissolved form has been found to vary from 4:1 in rural streams to 27:1 in urban streams (EPA 1986a).

In general, the highest lead concentrations are found in aquatic and terrestrial organisms that live near mining, smelting, and refining activities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage, sludge, and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting (lead source from spent shot); and in urban and industralized areas (Eisler 1988). Lead does not appear to be biomagnified in food chains, yet it may accumulate in plants (e.g., fungi, mosses, lichens, vascular plants, freshwater algae) and animals (e.g., earthworms, millipedes, woodlice, terrestrial birds and mammals, freshwater invertebrates, and fish). In aquatic organisms, lead concentrations are usually highest in benthic organisms and algae, and lowest in upper-trophic-level predators (e.g., carnivorous fish). High bioconcentration factors (BCFs) were determined in studies using oysters (6,600 for *Crassostrea virginica*), freshwater algae (92,000 for *Senenastrum capricornutum*), and marine algae (13,000-82,000 in various species found in Raritan Bay, New Jersey).

In water, tetraethyl and tetramethyl lead are susceptible to significant hydrolysis, with the rate of degradation accelerated by seawater. Removal of tetraalkyl lead compounds from seawater occurs at rates that provide half-lives measurable in days (DeJonghe and Adams 1986). Degradation proceeds from trialkyl lead to dialkyl lead to inorganic lead; in seawater, the initial degradation product is trialkyl chloride. Tetraethyl and tetramethyl lead are also susceptible to significant photolytic decomposition in water. Photolysis of tetraethyl lead can produce triethyl lead, which may be more persistent in the environment than tetraethyl lead. In aqueous solution, tetraethyl and tetramethyl lead can be adsorbed by suspended particulate matter and sediment, which may extend the length of their persistence in water. Bioaccumulation of tetraethyl lead in aquatic organisms has been demonstrated (EPA 1985a).

6.3.3 Soil

The accumulation of lead in most soils is primarily a function of the rate of deposition from the atmosphere. Most lead is retained strongly in soil, and very little is transported into surface water or groundwater (EPA 1986a, NSF 1977). The fate of lead in soil is affected by the specific or exchange adsorption at mineral interfaces, the precipitation of sparingly soluble solid phases, and the formation of relatively stable organic-metal complexes or chelates with soil organic matter. These processes are dependent on such factors as soil pH, organic content of soil, the presence of inorganic colloids and iron oxides, ion-exchange characteristics, and the amount of lead in soil

(NSF 1977). There is evidence that atmospheric lead enters the soil as lead sulfate, or it is converted rapidly to lead sulfate at the soil surface. Lead sulfate is relatively soluble, and thus could leach through soil if it were not transformed. In soils with pH of ≥5 and with at least 5% organic content, atmospheric lead is retained in the upper 2 to 5 cm of undisturbed soil. Because many plants commonly take up lead from soil, unless plants are harvested or removed, lead may eventually be returned to soil when these plants decay (EPA 1986a).

Lead has a high degree of immobility in most soils (NSF 1977). However, mobilization of lead from soil may occur as a result of runoff of lead-bearing soil particles to surface waters during heavy rain. The mobilization of lead from soil to the atmosphere may also occur by downwind transport of smaller surfacial lead-containing soil particles entrained in the prevailing wind (NSF 1977). This process may be important in contributing to the atmospheric burden of lead around some lead-smelting and Superfund (NPL) sites that contain elevated levels of lead in soil. The downward movement of lead from soil by leaching is very slow under most natural conditions (NSF 1977). The conditions that will induce leaching are the presence of lead in soil at concentrations that either approach or exceed the sorption capacity of the soil, the presence of materials in soil that are capable of forming soluble chelates with lead, and a decrease in the pH of the leaching solution (for example, acid rain) (NSF 1977). Partial favorable conditions for leaching may be present in some soils near lead-smelting and Superfund sites.

Limited data indicate that tetraethyl and tetramethyl lead are converted into water soluble lead compounds in soil. Although tetraethyl and tetramethyl lead are not expected to leach significantly through soil, their water soluble metabolites may be subject to leaching (EPA 1985a).

7. POTENTIAL FOR HUMAN EXPOSURE

7.1 OVERVIEW

Lead is a naturally occurring element which is dispersed throughout the environment primarily as the result of anthropogenic activities. Environmental fate processes may transform one lead compound to another; however, lead itself is not degraded and is still available for human exposure.

The general population is exposed to lead in ambient air, in many foods, in drinking water, and in dust. Segments of the general population at highest risk of health effects from lead exposure are preschool-age children, pregnant women and their fetuses, and white males between 40 and 59 years of age. Within these groups, relationships have been established between lead exposure and adverse health effects.

The average baseline intake of lead for 1982-83 by 2-year-old children, adult females, and adult males has been estimated to be 46.6, 37.5, and 50.7 μg/day, respectively. These baseline values (described in detail in Tables 7.1 and 7.2) reflect minimum levels of exposure during normal daily living and are based on individuals who live and work in a nonurban environment, eat a normal diet of food taken from a typical grocery shelf, engage in normal mouthing behavior (in the case of children), and have no habits or activities that would tend to increase lead exposure. Additional exposure above baseline levels is common. Some of the more important additional lead exposures occur due to residence in an urban environment, residence near stationary sources (e.g., smelters), consumption of produce from family gardens, renovation of homes containing lead-based paint, pica (an abnormal eating habit), interior lead paint dust, occupational exposure, secondary occupational exposure, smoking, and wine consumption. Higher than normal exposures may also occur to residents living in close proximity to Superfund (NPL) sites that contain elevated levels of lead. At this time, lead and lead compounds have been found at 635 out of 1,177 sites on the National Priorities list of hazardous waste sites in the United States. As more sites are evaluated by the Environmental Protection Agency (EPA), this number may change. The occurrence of these sites is shown in Fig. 7.1 (View 1989). The highest and most prolonged lead exposures are found among workers in the lead-smelting, refining, and manufacturing industries.

7.2 LEVELS MONITORED IN THE ENVIRONMENT

7.2.1 Air

Lead levels in the ambient air have been monitored in a number of remote, urban, and nonurban areas of the United States and the world

Table 7.1. Summary of base-line human exposure to lead (μg/day)

Source	Total lead consumed	Soil		Direct atmospheric lead[a]	Lead from solder or other metals	Lead of undetermined origin
		Natural lead consumed	Indirect atmospheric lead[a]			
Child, 2 years old						
Inhaled air	0.5	0.001		0.5		
Food, water, and beverages	25.1	0.71	1.7	10.3	11.2	1.2
Dust	21.0	0.6		19.0		1.4
Total	46.6	1.3	1.7	29.8	11.2	2.6
Percent	100%	2.8%	3.5%	64.0%	24.0%	5.6%
Adult female						
Inhaled air	1.0	0.002		1.0		
Food, water, and beverages	32.0	0.91	2.4	12.6	8.2	1.5
Dust	4.5	0.2		2.9		1.4
Total	37.5	1.2	2.5	17.4	13.5	2.9
Percent	100%	3.1%	6.6%	46.5%	36.1%	7.8%
Adult male						
Inhaled air	1.0	0.002		1.0		
Food, water, and beverages	45.2	1.42	3.5	19.3	18.9	2.2
Dust	4.5	0.2		2.9		1.4
Total	50.7	1.6	3.5	23.2	18.9	3.6
Percent	100%	3.1%	6.8%	45.8%	37.2%	7.0%

[a]Indirect atmospheric lead has been previously incorporated into soil and will probably remain in the soil for decades or longer. Direct atmospheric lead has been deposited on the surfaces of vegetation and living areas or incorporated during food processing prior to human consumption.

Source: EPA 1986a.

Table 7.2. Summary of potential additive exposures to lead (μg/day)

Exposure	Total lead consumed	Atmospheric lead consumed	Other lead sources
	Child		
Base-line exposure			
Inhaled air	0.5	0.5	
Food, water, and beverages	25.1	10.3	14.8
Dust	21.0	19.0	2.0
Total base line	46.6	29.8	16.8
Additional exposure			
Urban atmospheres[a]	91	91	
Family gardens[b]	48	12	36
Interior lead paint[c]	110		110
Residence near smelter[d]	880	880	
secondary occupational[e]	150		
	Adult male		
Base-line exposure			
Inhaled air	1.0	1.0	
Food, water, and beverages[f]	45.2	19.3	25.9
Dust	4.5	2.9	1.6
Total base line[f]	50.7	23.2	27.5
Additional exposure			
Urban atmospheres[a]	28	28	
Family gardens[b,f]	120	30	90
Interior lead paint[c]	17		
Residence near smelter[d]	100	100	
Occupational[g]	1,100	1,100	
Secondary occupational[e]	44		
Smoking[h]	30	27	3
Wine consumption[i]	100	?	?

[a] Includes lead from household (1,000 μg/g) and street dust (1,500 μg/g) and inhaled air (0.75 μg/m^3).

[b] Assumes soil lead concentration of 2,000 μg/g; all fresh leafy and root vegetables, and sweet corn replaced by produce from garden. Also assumes 25% of soil lead is of atmospheric origin.

[c] Assumes household dust rises from 300-2,000 μg/g. Dust consumption remains the same as base line.

[d] Assumes household and street dust increase to 10,000 μg/g.

[e] Assumes household dust increases to 2,400 μg/g.

[f] Values modified to reflect data presented in Table 7.1 and/or conclusions provided in the text of EPA 1986a.

[g] Assumes 8-h shift at 10 μg lead/m^3 or 90% efficiency of respirators at 100 μg lead/m^3, and occupational dusts at 100,000 μg/m^3.

[h] One and a half packs per day.

[i] Assumes unusually high consumption of 1 L/day.

Source: EPA 1986a.

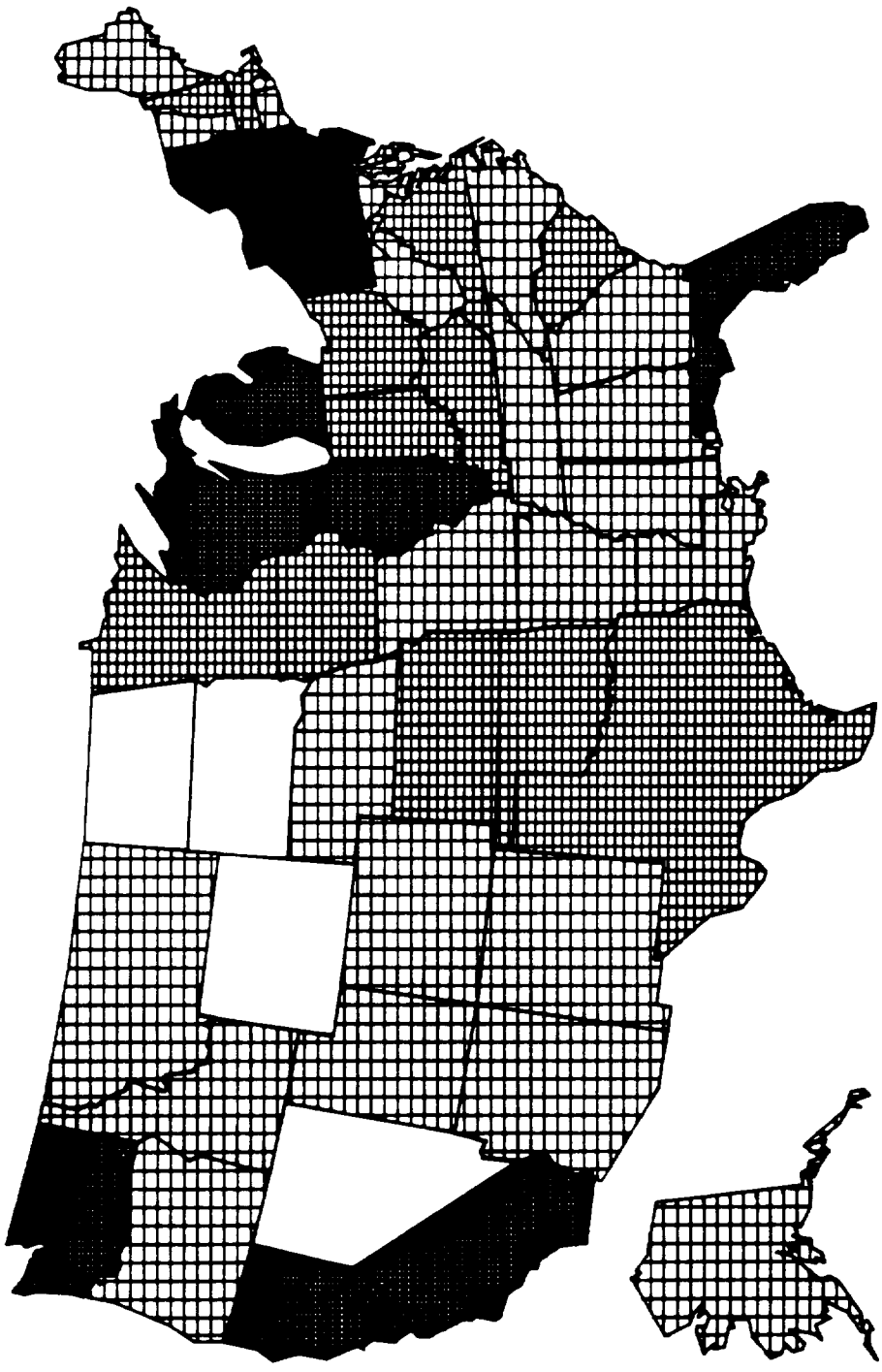


Fig. 7.1. Frequency of sites with lead contamination.

(EPA 1986a). Air lead concentrations vary widely but usually decrease with vertical and horizontal distance from emission sources; they are generally 0.3 to 0.8 times lower indoors than outdoors. Levels of lead in ambient air range from 0.000076 $\mu g/m^3$ in remote areas to >10 $\mu g/m^3$ near stationary sources such as smelters. Unusually high levels may be found in areas of high traffic density and in confined places, such as parking garages and tunnels, where auto exhaust is found. Monitoring data from a composite of 147 sampling sites throughout the United States indicate that the maximum quarterly average lead level in urban air during 1984 was 0.36 $\mu g/m^3$. Because consumption of leaded gasoline has been reduced drastically in recent years (an estimated 95% between 1984 and 1987), the current atmospheric concentrations of lead in urban areas without point source contributions are probably significantly lower than levels indicated by the monitoring data in EPA (1986a).

As indicated in Tables 7.1 and 7.2, the baseline value for daily intake of lead during 1982-83 by inhalation has been estimated to be 0.5 μg/day for a 2-year-old child and 1.0 μg/day for adults. The base-line estimate for adults assumes a 2-h/day exposure to an outside lead concentration of 0.75 $\mu g/m^3$, a 20-h/day exposure to an indoor lead concentration of 0.6 $\mu g/m^3$, a 2-h/day exposure to 5 $\mu g/m^3$ in high traffic, and an average daily intake of air by an adult of 20 m^3 (EPA 1986a).

Drastic reductions in the lead content of gasoline since 1982-83 have resulted in a notable decrease in lead emissions to the atmosphere. As a result, the current baseline level of lead intake by inhalation is thought to be markedly lower than 1982-83 levels.

7.2.2 Water

Lead has been monitored in surface water, groundwater, and drinking water, and in sediments throughout the United States and the world. The concentration of lead in surface water is highly variable depending upon sources of pollution, lead content of sediments, and characteristics of the system (pH, temperature, etc). Levels of lead in surface waters throughout the United States typically range between 5 and 30 $\mu g/L$, although levels as high as 890 $\mu g/L$ have been measured (EPA 1986a). Levels of lead in seawater are ~0.005 $\mu g/L$ (Perwak et al. 1982). Lead concentrations in surface water are higher in urban areas than those in rural areas (Perwak et al. 1982). Sediments contain considerably higher levels of lead than corresponding surface waters. The average lead content of river sediments is estimated to be ~20 mg/kg, while the average level in coastal sediments is ~100 mg/kg (Perwak et al. 1982). The typical concentration of lead in groundwater has been found to range between 1 and 100 $\mu g/L$ (EPA 1986a).

EPA (1988b) estimated that 99% of the 219 million people in the United States using public water supplies are exposed to distributed water with levels of lead <0.005 mg/L, and about ~2 million people are served by distributed water with levels of lead >0.005 mg/L.

Lead levels ranging between 0.01 mg/L and 0.03 mg/L on average can be found in households, schools, and office building drinking water due to plumbing corrosion and subsequent leaching of lead. The combination of corrosive water and lead pipes or lead soldered joints in the distribution system or houses can create localized zones of high lead concentrations >0.50 mg/L (EPA 1989b).

7.2.3 Soil

The lead content of soil derived from crustal rock typically ranges from <10 to 30 μg Pb/g soil. However, the concentration of lead in the top layers of soil varies widely due to deposition and accumulation of atmospheric dust from anthropogenic sources. The concentration of soil lead generally decreases as distance from contaminating sources increases. Next to roadways it is estimated that the levels of lead in soil are typically 30-2,000 μg/g higher than natural levels, while soils adjacent to roads that been traveled since 1930 have been enriched by as much as 10,000 μg/g (EPA 1986a). Soils adjacent to houses with exterior lead-based paints may have lead levels of >10,000 μg/g (EPA 1986a). In urban areas and in sites adjacent to smelters, lead levels ranging from 10 to 60,000 μg/g soil have been measured in the upper layer of soil (EPA 1986a).

Results of studies carried out in Baltimore, Maryland, and in Minnesota indicate that within large light-industrial urban settings, the highest soil lead levels generally occur in inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1984, 1985, in press 1989). Median soil lead levels found during the Minnesota study ranged from 20 to 700 μg/g soil. Levels varied depending upon the location (foundation, yard, street side) where the soil samples were collected (Mielke et al. in press 1989).

7.2.4 Other

Typical concentrations of lead in various foods are: dairy products, 0.003 to 0.083 μg/g; meat, fish, and poultry, 0.002 to 0.159 μg/g; grain and cereal products, 0.002 to 0.136 μg/g; leafy vegetables, 0.011 to 0.649 μg/g; fruits, 0.006 to 0.223 μg/g; oils, fats, and shortenings, 0.002 to 0.028 μg/g; sugar and adjuncts, 0.006 to 0.073 μg/g; beverages, 0.002 to 0.041 μg/L (EPA 1986a). Canning foods in lead-soldered cans can increase levels of lead eight- to tenfold; however, the impact of canning appears to be decreasing since there has been a decrease in the use of lead-soldered cans. Based on recently published data provided by the Food and Drug Administration (FDA), the following are the baseline values for average daily intake of lead by consumption of food, water, and beverages: 25.1 μg/day for 2-year-old children; 32.0 μg/day for adult males; and 45.2 μg/day for adult females (see Tables 7.1 and 7.2). As a result of the decrease in the use of lead-soldered food cans, the current baseline intake of lead by consumption of food, water, and beverages is probably lower than these estimates. Additional exposure to lead through dietary intake by people living in an urban environment is estimated to be ~28 μg/day for adults and 91 μg/day for children, all of which can be attributed to atmospheric lead (dust). Atmospheric lead may be added to food crops in the field or garden (through uptake from soil and from direct deposition

onto crops), during transport to market, during processing, and during kitchen preparation (EPA 1986a).

Another source of dietary lead is the use of inadequately glazed earthenware vessels for food storage and cooking. Because of the number of incidences of lead poisoning that have resulted from the use of earthenware vessels, the U.S. Food and Drug Administration (FDA) has established a limit for the allowable amount of leachable lead in earthenware vessels. However, inadequately glazed pottery manufactured in other countries continues to pose a significant health hazard. Likewise, homemade or craft pottery and procelain-glazed vessels have been found to release large quantities of lead, particularly if the glaze is chipped, cracked, or improperly applied. In addition, glaze on vessels that are repeatedly washed may deteriorate, and a vessel that previously met FDA standards may become unsafe (CDC 1985, EPA 1986a).

The lead content of dusts can be a significant source of exposure, particularly for young children. Base-line estimates of potential human exposure to dusts including intake due to normal hand-to-mouth activity are provided in Table 7.3. As indicated in Table 7.3, 45% of the baseline consumption of lead by children is estimated to result from the consumption of 0.1 g of dust/day. It is believed that ingestion of dust by children most commonly occurs as the result of mouthing hands, toys, and food that have come into contact with lead-containing surface dust, and less commonly by deliberate ingestion of soil (Bornschein et al. 1986). In estimating the baseline exposure to lead, it was assumed that, due to normal hand-to-mouth activity, children ingest 5 times as much dust as adults, with most of the excess coming from dusts from sidewalks and playgrounds (EPA 1986a).

Flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, are major sources of lead exposure for young children residing in these houses, particularly for children with pica (i.e., the compulsive, habitual consumption of nonfood items) (Bornschein et al. 1986, EPA 1986a). Lead concentrations of 1,000 to 5,000 $\mu g/cm^2$ have been found in chips of lead-based paint pigments, suggesting that consumption of a single chip of paint would provide greater short-term exposure than any other source of lead (EPA 1986a). It is estimated that between 40 and 50% of currently occupied housing in the United States may contain lead-based paint on exposed surfaces (Chisolm 1986).

In an attempt to reduce the amount of exposure due to deteriorating leaded paint, paint is commonly removed from homes by burning (gas torch or hot air gun), scraping, or sanding. These activities have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. In addition, those individuals involved in the paint removal process (i.e., do-it-yourself renovators and professional deleaders) can be exposed to such excessive levels that lead poisoning may occur (Rabinowitz et al. 1985, Fischbein et al. 1981, Chisolm 1986, Feldman 1978).

Lead is also present in cigarette smoke at a concentration that corresponds to ~2.5 to 12.2 μg/cigarette; ~2 to 6% of this lead may be inhaled by the smoker (EPA 1986a).

Table 7.3. Current base-line estimates of potential human exposure to dusts

	Dust lead concentration (μg/g)	Dust ingested (g/day)	Dust lead consumed (μg/day)	Source of lead		
				Natural (μg/day)	Atmospheric (μg/day)	Undetermined (μg/day)
Child						
Household dust	300	0.05	15	0.5	14.5	0.0
Street dust	90	0.04	4.5	0.0	4.5	0.0
Occupational dust	150	0.01	1.5	0.1	0.0	1.4
Total		0.10	21.0	0.6	19.0	1.4
Percent			100%	2.8%	90.5%	6.7%
Adult						
Household dust	300	0.1	3	0.1	2.9	0.0
Street dust	90	0.0	0	0.0	0.0	0.0
Occupational dust	150	0.01	1.5	0.1	0.0	1.4
Total		0.02	4.5	0.2	2.9	1.4
Percent			100%	4.5%	64.4%	31.1%

Source: EPA 1986a.

Cases of lead poisoning have been related to less common sources of exposure including the sniffing of gasoline vapors, consumption of illicit "moonshine" whiskey, and use of lead ammunition. Chronic gasoline sniffing has been recognized as a problem habit among children in rural and remote areas. When such practices involve leaded gasoline, the potential for lead intoxication exists. Illicit "moonshine" whiskey made in stills composed of lead-soldered parts (e.g., truck radiators) contains variable levels of lead. Moonshine has been found to contain up to 74 mg/L of lead. Use of lead ammunition may result in exposure to lead dust generated during gun or rifle discharge, lead pellets ingested or embedded in animals that are used as food sources, and lead pellets embedded in humans as a result of shooting accidents (EPA 1986a, Johnson and Mason 1984).

7.3 OCCUPATIONAL EXPOSURES

The National Institute for Occupational Safety and Health (NIOSH) has estimated that >1 million American workers are occupationally exposed to inorganic lead in >100 occupations (NIOSH 1977h, 1978b). The highest and most prolonged lead exposures are found among workers in the lead smelting, refining, and manufacturing industries. In work areas, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. Airborne dusts settle onto food, water, clothing, and other objects, and may subsequently be transferred to the mouth. Therefore, good housekeeping and good ventilation have a major impact on the extent of exposure. While occupational exposure is widespread, environmental monitoring data on levels of exposure in many occupations are not available. This is partly because lead exposure is frequently monitored by biological testing (e.g., determination of urinary lead levels, blood lead levels, urinary coproporphyrin levels, or delta-aminolevulinic acid levels) rather than monitoring the workplace environment for lead concentrations (NIOSH 1978b, EPA 1986a).

Potentially high levels of lead may occur occupationally, as follows: in lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops and other industries requiring flame soldering of lead solder, and gas stations (EPA 1986a, Feldman 1978, Goldman et al. 1987, NIOSH 1978b). Workers involved in the production of gasoline additives, tetraethyl lead and tetramethyl lead, are exposed to both inorganic lead and lead alkyls. The major potential hazard to these workers appears to be from dermal exposure (EPA 1986a).

Secondary occupational exposure may occur among families of workers who inadvertently bring home lead dusts on clothing worn at work. Blood lead levels have been found to be markedly higher in household members residing in homes of occupationally exposed workers compared to members of homes of people not occupationally exposed (EPA 1986a, Grandjean and Bach 1986).

7.4 POPULATIONS AT RISK

As discussed by EPA (1986a), at least three groups of populations at risk can be identified: preschool-age children, fetusus, and white males between 40 and 59 years of age.

Young children are inherently more susceptible to the effects of lead because of the greater intake of lead by infants and young children in the respiratory and gastrointestinal tracts on a body-weight basis compared with adults; the greater absorption and retention rates of lead in children; a greater prevalence of nutrient deficiency, which can affect gastrointestinal lead absorption; normal hand-to-mouth activity and pica; differences in the efficiency of lead sequestration in bone; and incomplete development of the blood-brain barrier increasing the risk of entry of lead into the nervous system (EPA 1986a).

The American Academy of Pediatrics (1987) has concluded that lead continues to be a significant hazard to the health of children in the United States because most children in this country are exposed to lead due to contamination of air, dust, and soil through combustion of leaded gasoline. In addition, many children are at risk for ingestion of lead-based paint and of soil and dust contaminated through the deterioration of lead-based paint.

Fetuses are at even greater risk. As discussed in Sect. 4.2.2 on distribution and body burden in the Toxicological data section, lead can readily cross the placental barrier; therefore, exposure of women to lead during pregnancy results in uptake by the fetus. Furthermore, since the physiological stress of pregnancy may result in mobilization of lead from maternal bone, fetal uptake of lead can occur from a mother who was exposed to lead before pregnancy, even if no lead exposure occurs during pregnancy. Prenatal exposure may be related to postnatal mental retardation, impaired postnatal neurobehavioral development, and reduced birth weight and gestational age (EPA 1986a).

Increased blood pressure is associated with blood lead concentrations possibly as low as 7 μg/dL. It appears that this relationship is particularly significant for middle-aged white males (aged 40 to 59) (EPA 1986a).

8. ANALYTICAL METHODS

Because lead is ubiquitous in the environment and in human tissues, and because it is one of the earliest identified toxic elements known to man, there are a vast number of analytical methods available for the analysis of lead in both environmental and biological media. The popular methods of the past (e.g., colorimetric methods) are rarely used now because of inadequate sensitivity, lack of reliability, and unsatisfactory turnaround time. The methods most commonly used today are electrothermal atomic absorption spectrometry (EAAS), anode stripping voltammetry (ASV), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and X-ray fluorescence spectroscopy (XRF). With the availability of commercial autosamplers, the reproducibility of EAAS has been greatly improved. According to Grandjean and Olsen (1984), EAAS and ASV are the methods of choice for the analysis of lead. Other specialized methods for lead analysis are proton-induced X-ray emission (PIXE), fast neutron activation analysis (FNAA), mass spectrometry (MS), and microwave plasma detection (MPD) (Berg and Jonsson 1984, Grandjean and Olsen 1984). The most reliable method for the determination of lead at low concentrations is isotopic dilution mass spectrometry (IDMS) (EPA 1986a, Grandjean and Olsen 1984), but few laboratories require such sophisticated methods for the routine analysis of lead.

Results of lead analyses from numerous laboratories often do not agree (Fell 1984). Certified standard reference materials (SRMs) are required for monitoring the accuracy of lead analysis. A few SRMs, e.g., orchard leaves and bovine liver, are available from the National Bureau of Standards (NBS). A certified porcine blood (SRM 955) has recently been made available by NBS. Certified blood samples are also available from a few commercial facilities (EPA 1986a). The most comprehensive proficiency testing program for lead analysis is being carried out by the CDC of the U.S. Public Health Service (EPA 1986a, Grandjean and Olsen 1984). Currently the testing is being conducted by the American Association of Clinical Chemists, the American Association of Bioanalysts, and a few states, including California.

8.1 ENVIRONMENTAL MEDIA

The sampling, storage, and sample handling prior to sample analysis require a rigorous quality assurance program in order to ensure the validity of reported results. The details of methods of sampling, storage, sample handling, and analysis of lead in different environmental media are given by EPA (1986a). The methods for particle sizing of atmospheric lead, sampling methods for lead in dry deposition, stationary, and mobile sources are also given by EPA (1986a). In determining the lead concentrations in the atmosphere, a distinction between the concentration of lead in the particulate and gaseous forms

is often necessary. Details of sampling, storage, and analytical methods for organolead compounds and the analytical methods for the differentiation of various species of organoleads are reported in DeJonghe and Adams (1986), Berg and Jonsson (1984), and EPA (1986a). Duggan and Inskip (1985) discuss lead sampling and analysis in soils and dusts. In determining lead concentrations in aquatic media, a distinction between dissolved and particulate lead is often required. Details of such methods are available in EPA (1986a). A brief description of the commonly used methods for the determination of lead in different environmental media is given in Table 8.1.

8.2 BIOLOGICAL SAMPLES

The detailed methods for sampling, storage, sample handling, and analysis of lead in biological media are provided by EPA (1986a) and Grandjean and Olsen (1984). Some of the common methods for lead quantitation in biological media are listed in Table 8.1.

Analyses of lead concentration in blood, urine, and bone have been used as an indication of exposure to lead. Measurement of lead in blood is the most common method of assessing exposure. The ACGIH (American Conference of Governmental Industrial Hygienists) has recommended a Biological Exposure Index (BEI) for lead of 50 μg/100 mL in blood and 150 μg/g creatinine in urine. For the implementation of BEI, ACGIH recommends quantification of blood lead by the flameless atomic absorption method. In the case of urine, chelation, solvent extraction, followed by atomic absorption for quantification, is the recommended method. If the recommended BEIs are exceeded repetitively, lead poisoning is likely to develop. The BEIs are not protective of fetuses or of children (ACGI 1986).

As seen from Table 8.1, the limit of detection of lead in blood is 3 to 5 μg/dL, although the detection limit can be lowered with less common methods, such as differential pulse anode stripping voltammetry. The lead level in urine is of questionable value as an indicator of exposure because of the lack of correlation between urinary lead levels and CNS effects and the low variable lead excretion in urine (Jensen 1984). The determination of urinary chelatable lead (with calcium disodium EDTA), although cumbersome and perhaps unsafe (Cory-Slechta et al. 1987), may be a good indicator of lead stored in body tissues (Janin et al. 1985, Ibels and Pollock 1986); however, this method ignores the relatively inaccessible lead stored in bone and does not account for the impact of a recent large exposure that may not yet have reached equilibrium with the fixed organ soft tissue compartments. A noninvasive method using X-ray fluorescence can be used for the determination of lead concentration in bones, and the method has been reported to be a better indicator of stored lead in body tissue (Ahlgren et al. 1976, Bloch et al. 1976, Rosen et al. 1987). Even at the present time, the matrix blood is used widely as an indicator of lead toxicity (Ibels and Pollock 1986).

In addition to the chemical methods, a number of biochemical assays are available for the assessment of lead toxicity in the human body. Details of such assays are reported in Grandjean and Olsen (1984), Stokinger (1981), and EPA (1986a). The commonly used assays are urinary

coproporphyrin and delta-aminolevulinic acid (ALA), plasma delta-aminolevulinic acid, 3',5'-nucleotidase activity, delta-aminolevulinic dehydrase (ALA-D), and erythrocyte porphyrin (EP) either in the free form (FEP) or as zinc protoporphyrin (ZPP). The ALA-D and the FEP (or ZPP) methods appear to be most sensitive. The spectrofluorometric methods for the determination of FEP and ZPP are given in EPA (1986a). Other biological assays that have been used as indicators of lead exposure are serum immunoglobulins and salivary IgA (Ewers et al. 1982); however, not all the biological assays are specific for lead (Grandjean and Olsen 1984). Discussions of the correlation between lead exposure and data from human biomonitoring can be found in Sect. 2.3.3.2 on adequacy of the database in the Health effects summary section.

Table 8.1. Analytical methods for determining lead concentrations

Sample matrix	Sample preparation	Analytical method[a]	Detection limit	Accuracy/ % recovery	References
Occupational air (particulate lead)	Particulate matter collected on membrane filter wet ashed; aliquots introduced in graphite furnace	EAAS (NIOSH method P&CAM 214)	<0.02 mg/m^3 for 5 L air	NR[b]	NIOSH 1977a
	Particulate matter collected on membrane filter wet ashed; buffered solution analyzed	ASV with mercury-graphite electrode (NIOSH method 7082)	0.16 μg/m^3 for 100 L air	NR	NIOSH 1977b
	Particulate matter collected on membrane filter wet ashed and aspirated into AA unit	AAS flame (NIOSH method S341 and P&CAM 173)	2.6 μg/sample	100	NIOSH 1977c,d
	Particulate matter collected on cellulose acetate filter wet ashed and nebulized for analysis	ICP/AES (NIOSH method P&CAM 351)	<5 μg/m^3 for 500 L air	95–105 at 5 μg/m^3 to 2 mg/m^3	NIOSH 1984
Occupational air (tetraethyl and tetramethyl lead)	Particulate filtered sample adsorbed on XAD-2, desorbed by solvent extraction	GC/PID (NIOSH method S383 and S384)	40 μg/m^3 (Me_4Pb) 45 μg/m^3 (Et_4PB)[c]	99 94.5	NIOSH 1978a
Ambient air (particulate and gaseous lead)	Particulate matter collected on glass fiber filter; filtered gases passed through iodine monochloride bubblers; particulate matter wet ashed; bubbler solution converted to dithizone complex in presence of EDTA-salts and extracted with CCl_4	AAS (particulate) EAAS (gaseous)	0.10 μg/m^3 0.25 ng/m^3	93 97–99 (gaseous)	EPA 1986a, Scott et al. 1976, Birch et al. 1980
	Particulate matter collected on nucleopore filters; filtered gases cryogenically trapped and thermally desorbed	XRF (particulate) GC/EAAS (gaseous)	0.3 μg/m^3 0.2 ng/m^3	46–>90 90–100	DeJonghe et al. 1981

Table 8.1 (continued)

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy/ % recovery	References
Soil, wastes, and groundwater	Sample acid digested, diluted with water, and filtered	AAS with background correction (EPA method 7420)	0.1 mg/L[d]	NR	EPA 1982a
		EAAS with background correction (EPA method 7421)	1 μg/L[d]	NR	
Milk	50 μL $(C_2H_5)_4NOH$ in ethanol added to 25 μL milk, heated, and diluted with water to 125 μL	EAAS	NR	NR	Michaelson and Sauerhoff 1974
Mussel, shrimp, and plaice	Sample purged at 100°C, sorbed in trap, and thermally desorbed (tetraalkyl lead)	GC/AAS	0.1 ng/g	NR	Chau et al. 1980
Agricultural crops	Sample dry ashed with H_2SO_4 and HNO_3 and diluted with water	DPASV	2 ng/g	85–106	Satzger et al. 1982
Blood (whole)	Sample wet ashed with acid mixtures; residue dissolved in dilute $HClO_4$	ASV with mercury-graphite electrode (NIOSH method P&CAM 195)	0.04 mg/L	95–105	NIOSH 1977e
	Sample wet ashed with HNO_3; residue dissolved in dilute HNO_3	EAAS (NIOSH method P&CAM 214)	0.1 mg/L for 1 mL sample	NR	NIOSH 1977a
Blood and urine	Sample wet ashed with HNO_3, chelated with APDC[e], and extracted with MIBK[f]	AAS (NIOSH method P&CAM 262)	50 μg/L (blood) 10 μg/L (urine)	99 (blood) NR (urine)	NIOSH 1977f
	Sample wet ashed with HNO_3, complexed with diphenylthiocarbazone, and extracted with chloroform	Spectrophotometry (NIOSH method P&CAM 102)	30 μg/L (blood) 12 μg/L (urine)	97 97	NIOSH 1977g

Table 8.1 (continued)

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy/ % recovery	References
Ambient air (organolead)	Sorbed on cooled XAD-4 and thermal desorption	HRGC/MS	NR	NR	DeJonghe and Adams 1986, Berg and Johansson 1984
Water and wastewater	Filtered through a 0.45-μm membrane filter (dissolved lead); filtered material dissolved by wet ashing (insoluble lead)	AAS (EPA method 239.1)	0.1 mg/L	99.8–125.7	EPA 1983
		EAAS (EPA method 239.2)	1 μg/L	88–95	
	Filtered through a 0.45-μm membrane filter (dissolved lead); filtered material dissolved by wet ashing (insoluble lead)	ICP-AES (EPA method 200.7)	42 μg/L	94–125	EPA 1983
Water	Sample collected on chelating resin (Chelex-100) filter and irradiated (dissolved lead)	XRF	NR	NR	IARC 1980
Seawater	Filtered water collected on chelating resin and eluted with acid (dissolved lead)	ICP-AES	1 μg/L	NR	IARC 1980
Water	Sample extracted with hexane (tetraalkyl lead)	GC/AAS	0.5 μg/L	88–90	Chau et al. 1979
	Sample complexed with diethyldithiocarbamate, extracted with pentane, dried, and butylated (ionic alkyl lead)	GC/AAS	~1 ng/L	90–108	Chakraborti et al. 1984
Soil	Sample dried, dry ashed, digested with acid, and diluted with water	AAS	2 mg/kg	79–103	Beyer and Cromartie 1987

Table 8.1 (continued)

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy/ % recovery	References
Blood and urine	Sample hemolyzed (not required for urine), complexed with APDC, and extracted with MIBK	AAS (NIOSH method P&CAM 208)	0.05 μg/g (blood) 0.05 μg/mL (urine)	95–105 (blood) NR (urine)	NIOSH 1977h
Urine	Sample wet ashed with acid mixture and dissolved in dilute $HClO_4$	ASV with mercury-graphite electrode (NIOSH method P&CAM 200)	4 μg/L for 1 mL sample	90–110	NIOSH 1977i
Blood and urine	^{206}Pb added and sample acid digested; lead coprecipitated by addition of $Ba(NO_3)_2$, followed by electrodeposition on platinum wire	MS	NR	98–99	Manton and Cook 1984
Serum and cerebrospinal fluid	^{206}Pb added and sample acid digested; lead separated by ion-exchange, eluted, and deposited onto platinum wire	MS	NR	80–120	Manton and Cook 1984
Hair	Sample ultrasonically cleaned with acetone and detergent (1% Triton X-100) and wet ashed with HNO_3	EAAS with background correction	NR	NR	Bonithon-Kopp et al. 1986
	Sample cleaned with hexane, ethanol, and water and wet ashed with HNO_3 and H_2O_2	ICP-AES	NR	NR	Thatcher et al. 1982
Teeth	Sample dry ashed, then wet ashed with HNO_3	AAS with background correction	NR	90–110 (estimated)	Steenhout and Pourtois 1981
Bone	Partially polarized photon directed at anteromedial skin surface of mid-tibia (non-invasive technique)	XRF	~2 μg/g	NR	Rosen et al. 1987

Table 8.1 (continued)

Sample matrix	Sample preparation	Analytical method	Detection limit	Accuracy/ % recovery	References
Spleen	Sample wet digested with HNO_3-$HClO_4$ mixture	EAAS with background correction	NR	NR	Blakley et al. 1982
Liver and kidney	Sample wet digested with HNO_3-$HClO_4$ mixture	EAAS with background correction	NR	NR	Blakley and Archer 1982
Tissues (brain, heart, lung, kidney, liver, and testes)	Sample dry ashed, then wet ashed with HNO_3	AAS with background correction	NR	NR	Exon et al. 1979
Brain	Sample wet ashed with mixture of acids, mixed with Metex change M, and analyzed	ASV	NR	NR	Jason and Kellogg 1981

[a]EAAS = electrothermal atomic absorption spectrometry; ASV = anode stripping voltammetry; AAS = atomic absorption spectrometry; ICP/AES = inductively coupled plasma/atomic emission spectroscopy; GC = gas chromatography; PID = photoionization detector; XRF = X-ray fluorescence; HRGC = high resolution gas chromatography; MS = mass spectrometry; DPASV = differential pulse anodic stripping voltammetry.

[b]NR = Not reported.

[c]Et = ethyl.

[d]The detection limits of these methods were determined with spiked distilled water.

[e]APDC = ammonium pyrrolidine dithiocarbamate.

[f]MIBK = methyl isobutyl ketone.

9. REGULATORY AND ADVISORY STATUS

9.1 INTERNATIONAL

The World Health Organization (WHO) has set the guideline value for lead in drinking water at 0.05 mg/L (WHO 1984). In a recent draft report on air quality guidelines, WHO identified 20 μg/dL as the blood lead level of concern (WHO 1986).

9.2 NATIONAL

9.2.1 Regulations

9.2.1.1 Air

EPA (1978) established national primary and secondary ambient air quality standards for lead of 1.5 $\mu g/m^3$, averaged over a calendar quarter (EPA 1978). These standards are currently under review for possible revision (EPA 1986a).

OSHA (1985) has set an action level of 30 $\mu g/m^3$ and a permissible exposure limit (PEL) of 50 $\mu g/m^3$, averaged over an 8-h work period, for employee exposure to airborne lead. For exposures >8 h, the maximum permissible concentration is calculated by dividing 400 $\mu g/m^3$ by the hours of exposure.

9.2.1.2 Water

EPA (1985b) has established a maximum contaminant level (MCL) for lead of 0.05 mg/L as an interim regulation. EPA (1985b) proposed a recommended maximum contaminant level (RMCL) of 0.02 mg/L. More recently, EPA (1988b) proposed an MCLG of 0 mg/L based on the following three factors: concern for effects in adults, children, and fetuses at blood lead levels of 10-15 μg/dL or lower; the EPA policy goal that lead contribution from drinking water to total exposure should be minimal because a substantial portion of a sensitive population (children) already has blood lead levels that exceed acceptable levels; and the EPA classification of lead as a Group B2 carcinogen. In addition, EPA (1988b) proposed new drinking water regulations as follows: (1) an MCL for lead in drinking water entering the distribution system (after any treatment) of 0.005 mg/L (5 μg/L), (2) an MCL for copper entering the distribution system of 1.3 mg/L, (3) either a requirement to obtain and implement a state-approved treatment plan to install optimal corrosion control or a demonstration that the system meets the "no-action" level for compliance with corrosion control (i.e., 95% of the samples at the tap have pH ≥8 and copper levels ≥1.3 mg/L and that the arithmetic average lead levels of the samples at the tap are ≥0.010 mg/L), and (4) a public education program if the arithmetic average lead level of

samples at the tap is >0.010 mg/L or if lead levels in >5% of the samples are >0.020 mg/L.

The Lead Contamination Control Act of 1988 mandates that the Consumer Product Safety Commission require the repair or recall of drinking water coolers containing lead in parts that come in contact with drinking water, prohibit the sale of drinking water coolers that are not lead-free, require that the states establish programs to assist educational agencies in testing and remedying lead contamination of drinking water in schools, require that the EPA certify testing laboratories, and provide for coordination by the CDC of grants for additional lead screening and referral programs for children and infants (Congressional Record 1988a,b).

Lead is regulated by the Clean Water Act Effluent Guidelines for the following industrial point sources: electroplating, organic chemicals, inorganic chemicals, iron and steel manufacturing, nonferrous metals manufacturing, steam electric, glass manufacturing, asbestos, rubber, timber products processing, metal finishing, mineral mining, ore mining, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, battery manufacturing, metal molding and casting, procelain enameling, copper forming, electrical and electronic components, and nonferrous metal forming (EPA 1988c).

9.2.1.3 Other

EPA (1982b) designated lead and compounds (not otherwise specified), lead acetate, lead phosphate, and lead subacetate as hazardous constituents of solid waste.

Federal law [CERCLA 103(a) and (b)] requires that the National Response Center be notified when there is a release of a hazardous substance in excess of the reportable quantity (RQ). RQ values for lead and lead components (EPA 1985c, 1986c) are as follows:

Compound	RQ (lb)
Lead (metallic) (diameter <100 μm)	1
Lead acetate (acetic acid, lead salt)	5,000
Lead arsenate	5,000
Lead chloride	100
Lead fluoroborate	100
Lead fluoride	100
Lead iodide	100
Lead nitrate	100
Lead phosphate	1
Lead stearate	5,000
Lead subacetate	1
Lead sulfate	100
Lead sulfide	5,000
Lead thiocyanate	100

Changes to the RQ values have been proposed for lead acetate, lead arsenate, lead phosphate, and lead subacetate; the RQ for lead

(metallic) is subject to change when the assessment of potential carcinogenicity and/or chronic toxicity is completed (EPA 1987).

The Consumer Product Safety Commission (CPSC 1977) noted that paint containing >0.5% lead and objects painted therewith had been banned under the Federal Hazardous Substance Act, effective in 1972 (FDA 1972). In 1977, the CPSC limited lead in most paints to 0.06%.

HUD has issued regulations requiring testing for and elimination of lead-based paint hazards in federally funded housing and housing rehabilitation programs, public housing, and Indian housing (HUD 1987a,b, 1988a). In addition, Sect. 566 of the 1988 Housing and Community Development Act directs HUD to carry out a lead abatement demonstration program to compare the relative cost-effectiveness and applicability of different methods to various types of housing (HUD 1988a). HUD (1988b) announced that the demonstration program was expected to be completed by December 1989.

EPA (1982c) introduced a regulation limiting the level of lead in leaded gasoline to 1.10 g/gallon as of November 1, 1982. The level of lead in unleaded gasoline was restricted to 0.05 g/gallon (EPA 1982c). EPA (1985d) subsequently reduced the level of lead permitted in leaded gasoline to 0.1 g/gallon effective January 1, 1986. An interim limit of 0.5 g/gallon was to have become effective July 1, 1985.

9.2.2 Advisory Guidance

9.2.2.1 Air

NIOSH (1978b) proposed a revised criterion for inorganic lead in air of 0.10 mg/m^3 (100 $\mu g/m^3$) as a TWA exposure for a 10-h workday. It was recommended that air levels be maintained so that blood lead levels not exceed 60 $\mu g/100$ g.

ACGIH (1987) recommended TWA-TLVs for lead and compounds as follows: inorganic lead, dust, and fumes, 0.15 mg/m^3 (150 $\mu g/m^3$ as lead); lead arsenate, 0.15 mg/m^3 (150 $\mu g/m^3$ as lead arsenate); lead chromate, 0.05 mg/m^3 (50 $\mu g/m^3$ as chromium).

9.2.2.2 Water

EPA (1980) recommended an ambient water quality criterion for lead (not otherwise specified) of 50 $\mu g/L$, the same as the current interim MCL mentioned above.

9.2.2.3 Other

To reduce the environmental level of lead to which children are exposed, CDC (1985) recommended that interior and exterior painted surfaces be tested for surface lead concentration using portable X-ray fluorescence. A four-step paint removal and replacement protocol was recommended for surfaces with lead levels ≥ 0.7 mg/cm^2. The CDC has also recommended that screening for lead poisoning should be incorporated into general pediatric health care programs, especially for children between the ages of 6 months and 9 years. Screening should be conducted for this age group at least once a year. Children having elevated blood lead levels (25 $\mu g/dL$ of whole blood or greater) and elevated EP levels

(35 μg/DL of whole blood or greater) should be clinically elevated for lead toxicity without delay.

9.2.3 Data Analysis

9.2.3.1 Reference doses (RfDs)

EPA has not derived a reference dose for oral exposure to lead.

9.2.3.2 Carcinogenic potency

Based on inadequate evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals, IARC (1987) classified lead and inorganic lead compounds in IARC Group 2B--possible human carcinogen.

Similarly, based on inadequate evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals, EPA (1988a) assigned lead and (inorganic) lead compounds an EPA classification of B2--probable human carcinogen. The EPA (1988a) recommended that a numerical estimate of cancer potency or risk based on animal dose-response data not be used because of the uncertainties, some of which may be unique to lead, involved in such an extrapolation. Current knowledge of the pharmacokinetics of lead indicates that an estimate derived by standard methods would not adequately delineate the potential risk (EPA 1988a).

9.3 STATE

Regulations and advisory guidance from the states were still being compiled at the time of printing.

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11. GLOSSARY

Acute Exposure--Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Bioconcentration Factor (BCF)--The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same time period.

Carcinogen--A chemical capable of inducing cancer.

Ceiling value (CL)--A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure--Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity--The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity--Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Frank Effect Level (FEL)--That level of exposure which produces a statistically or biologically significant increase in frequency or severity of unmistakable adverse effects, such as irreversible functional impairment or mortality, in an exposed population when compared with its appropriate control.

EPA Health Advisory--An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)--The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure--Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity--The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In vitro--Isolated from the living organism and artificially maintained, as in a test tube.

In vivo--Occurring within the living organism.

Key Study--An animal or human toxicological study that best illustrates the nature of the adverse effects produced and the doses associated with those effects.

Lethal Concentration(LO) (LC_{LO})--The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration(50) (LC50)--A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose(LO) (LD_{LO})--The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose(50) (LD50)--The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lowest-Observed-Effect Level (LOEL)--The lowest dose of chemical in a study or group of studies which produces statistically or biologically significant increases in frequency or severity of effects between the exposed population and its appropriate control.

Malformations--Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level--An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen--A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity--The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-Observed-Effect Level (NOEL)--That dose of chemical at which there are no statistically or biologically significant increases in frequency or severity of effects seen between the exposed population and its appropriate control.

Permissible Exposure Limit (PEL)--An allowable exposure level in workplace air averaged over an 8-h shift.

q_1^*--The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually $\mu g/L$ for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD)--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)--The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are: (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-h period.

Reproductive Toxicity--The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL)--The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity--This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen--A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)--A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-weighted Average (TWA)--An allowable exposure concentration averaged over a normal 8-h workday or 40-h workweek.

Uncertainty Factor (UF)--A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of humans, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX: PEER REVIEW

A peer review panel was assembled for lead. The panel consisted of the following members: Dr. J.J. Chisolm, Jr., Kennedy Institute for Handicapped Children, Baltimore, Maryland; Dr. D.A. Cory-Slechta, University of Rochester, Rochester, New York; and Dr. J.F. Rosen, Albert Einstein College of Medicine, Bronx, New York. These experts collectively have knowledge of lead's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Superfund Amendments and Reauthorization Act of 1986, Section 110.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

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